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NORTH AMERICAN AGRICULTURAL BIOTECHNOLOGY COUNCIL REPORT



NORTH AMERICAN AGRICULTURAL BIOTECHNOLOGY COUNCIL

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Providing an open forum for exploring issues in agricultural biotechnology

NABC REPORT 25

Biotechnology and North American Specialty Crops: Linking Research, Regulation, and Stakeholders

Proceedings of the twenty-fifth annual conference
of the North American Agricultural Biotechnology
Council, hosted by Texas A&M University,
June 4–6, 2013

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Allan Eaglesham and Ralph W.F. Hardy

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NABC Report 25

Biotechnology and North American Specialty Crops: Linking Research, Regulation, and Stakeholders

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NORTH AMERICAN AGRICULTURAL BIOTECHNOLOGY COUNCIL

Providing an open forum for exploring issues in agricultural biotechnology

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The twenty-fifth annual meeting of the North American Agricultural Biotechnology Council—"NABC 25"—was hosted by Bill McCutchen (executive associate director of Texas A&M AgriLife Research) at Texas A&M University, College Station, Texas. We thank Dr. McCutchen and his team for a most successful conference.

Thanks are due to the planning committee¹ (Rusty Carter, Heather Hirsch, Brenda Stone, Misty Vidrine, Carl Muntean, John Chivvis, Valerie Weber, Bill McCutchen, Bob Avant and Jackie Slovacek), to student workers (Maddie Kostroun, Cheyne Grey and Gus Sanchez) and to ANRP² student interns (Monica Hoz De Vila, Andrea Fonseca, Morgan Head, Dillon Garr, Shiloh Perry and Arlene Kent).

Smooth operation of the conference resulted from the contributions of the following:

Session Moderators: Dan Wineberger, David Baltensperger, Daniel Leskovar and Steve Pueppke.

Workshop Facilitators and Recorders: Peter Schuerman, Dan Lineberger, Daniel Leskovar, Frank Dainello, Bob Avant, Adam Helms and Andrea Kuban.

Student Voice Program Administrator: Susanne Lipari.

Student Voice Reporters: Matthew Bernard and Alma Laney.

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* * *

On behalf of NABC, we thank Graham Scoles (University of Saskatchewan) for first-rate leadership as NABC's chair, 2011–2013.

Ralph W.F. Hardy
President
NABC

Allan Eaglesham
Executive Director
NABC

December 2013

¹RWFH and AE also served on the planning committee.

²Agricultural and Natural Resources Policy Internship Program.

PREFACE

Taxpayers in the United States have invested heavily in public-sector research in agricultural biotechnology to provide more-sustainable and productive crops and safe and nutritious foods. Since the mid-1980s, scientists at the USDA and in university and small private laboratories have developed a broad range of genetically engineered (GE) varieties of specialty crops with useful traits including enhanced tolerances of biotic and abiotic stresses and improved nutrition¹. Almost a thousand different GE lines of small-market and specialty crops¹ were among the almost 17,000 regulated field trials approved by USDA since 1987².

In spite of this large public investment—as well as early technical successes and promising results in field trials—only a few GE specialty crops developed in public institutions have been released to date:

- Virus-resistant papaya
- A now defunct flax intended to be used for bioremediation
- Virus-resistant plum

These are very sparse returns considering substantial public investment over a quarter century. In fact, the majority of scientists at public institutions do not even consider further development of GE crops for commercial utility, even for traits that could advance agricultural systems, improve human health and help feed the increasing global population. On the other hand, there are signs that this trend is changing. Several transgenic events in specialty crops, are now moving towards commercialization as a result of collaborative efforts involving universities, industry, and regulatory agencies.

Furthermore, the Farm Bill—passed in February 2014—has restored the Specialty Crop Research Initiative funding, to about \$80 million per year³. We are pleased with this reemphasis of the fundamental importance of research in specialty crops, consistent with the focus of NABC's twenty-fifth annual conference.

NABC 25—held at Texas A&M University, College Station, June 4–6, 2013—brought together academic researchers, industry leaders, and government officials to discuss the roles of genomic sciences, regulatory policy and related topics in an attempt to catalyze increased agricultural progress, especially as it relates to specialty crops.

¹Miller J Bradford K (2010) The regulatory bottleneck for biotech specialty crops. *Nature Biotechnology* 28(10) 1012–1014.

²Anonymous (2014) Information Systems for Biotechnology: A National Resource in Agbiotech Information—USDA Field Tests of GM Crops. <http://gophisb.biochem.vt.edu/search-release-data.aspx>

³<http://www.thepacker.com/fruit-vegetable-news/Senate-passes-farm-bill-243553121.html#sthash.I9Xbcib1.dpuf>.

To foster discussion, NABC 25 was organized under five topics:

- Opportunities and Challenges for Specialty Crops
- Genetic Engineering and Specialty-Crop Improvement
- Case Studies
- The Regulatory Process and Technology Access
- Perspectives from Relevant Groups

The final session on the morning of the third day focused on “Next Steps.” Speakers Tony Shelton (Cornell), Thomas Redick (Global Environmental Ethics Counsel) and Neal Carter (Okanagan Specialty Fruits) formed a panel along with conference host Bill McCutchen (Texas A&M). The discussion, which involved audience contributions, was moderated by Steve Pueppke (Michigan State). Salient points emerging from the “Next Steps” exchanges are included in a “conference overview” chapter.

A poster session was held on the evening of the first day. Prizes totaling \$5,000 were awarded to the five best poster presentations (\$1,500–\$500).

Participants in the *Student Voice at NABC* program⁴ attended the keynote and plenary sessions and met as a group on the second evening to discuss issues that emerged from the conference subject matter.

This volume contains the conference overview, manuscripts generated from transcripts of the verbal presentations by the speakers (see Contents on pages ix–x for the full speaker list), transcripts of Q&A sessions, which included audience participation, the *Student Voice* report, and abstracts from the posters.

NABC’s twenty-sixth conference—*New DNA-Editing Approaches: Methods, Applications and Policy for Agriculture*—will be held October 8–9, 2014, in Ithaca, NY, hosted by Cornell University and the Boyce Thompson Institute.

Allan Eaglesham
Executive Director
NABC

Ralph W.F. Hardy
President
NABC

Figures are printed in grayscale, hence information may have been lost from graphics lifted from colored PowerPoint slides. Color versions of the figures are available at http://nabc.cals.cornell.edu/Publications/Reports/pubs_reports_25.htm.

⁴The *Student Voice at NABC* program provides grants of up to \$750 to graduate students at NABC-member institutions (one student per institution) to offset travel and lodging expenses. Also, registration fees are waived for grant winners. Information on the *Student Voice at NABC 26* will be available at <http://nabc.cals.cornell.edu/StudentVoice.htm>.

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PART I—CONFERENCE OVERVIEW

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Overview of NABC 25

Biotechnology and North American Specialty Crops: Linking Research, Regulation, and Stakeholders

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Specialty crops—fruits, vegetable, nuts (also turf and ornamentals)—are an important part of the human diet. In 2007, such crops represented approximately 40 percent of the \$140 billion in total agricultural receipts, despite being cultivated on just 4 percent of the total cropped area (Miller and Bradford, 2010; Alston and Pardey, 2008; USDA-NASS, 2009). Only six genetically engineered (GE) specialty crops are commercially available in the United States, whereas, in contrast, GE commodity crops—corn, soybean, cotton, canola, sugar beet—now dominate the markets in countries where they have been released. Possible reasons for this disparity are lack of research on specialty crops and/or a dearth of beneficial traits for crop improvement through genetic engineering. Alternatively, progression through the regulatory process may have failed (Miller and Bradford, 2010). To assess the R&D pipeline for GE specialty crops, Miller and Bradford (2010) conducted an extensive search for journal articles (January 2003–October 2008, 313 articles) describing work in specialty crops using recombinant DNA methods. Their data demonstrated a broad global research pipeline for GE specialty crops focused on traits potentially beneficial to producers and consumers. However, qualitative data revealed that although laboratory and field trials had been conducted on GE specialty crops in many countries, none had progressed to commercial production outside of the United States¹. Interviews with representatives of specialty crop-seed companies and nurseries provided extensive anecdotal evidence that potentially marketable GE products had been created and tested, but cost and uncertainty of the regulatory process had made further development uneconomical and precluded appraisal of market acceptance (Miller and Bradford, 2010).

¹With the possible exception of virus-resistant tomato and pepper in China.

A survey of NABC-member institutions in early 2013 confirmed the existence of several GE specialty crops, as did the above-described earlier worldwide study. Additional costs—beyond those required for varieties developed by “traditional” breeding—per insertion event associated with receiving regulatory approval have been assessed at \$1 million to \$15 million (Kalaitzandonakes *et al.*, 2007).

Although research on GE specialty crops continues to explore a range of beneficial applications their commercialization may depend upon a reexamination of the balance between potential risks versus benefits to society and adjustment in regulatory requirements (Miller and Bradford, 2010).

Advances in molecular genetics and genomics are providing new ways to help food production keep pace with global population growth. “Omics” technologies are becoming more rapid and more efficient, even as costs decrease. In spite of these advances—as discussed above—a majority of scientists at public US research institutions do not attempt to commercialize their GE crops even for traits that could help to feed hungry mouths and otherwise enhance human health.

NABC 25 was hosted by Texas A&M University, June 4–6, 2013. The conference—at the George Bush Presidential Library in College Station—brought together government officials, academic researchers and industry leaders, with the objective of encouraging the improvement and subsequent commercialization of specialty crops. Recent meetings with a similar theme include those convened by the American Association for the Advancement of Science (AAAS), *Whither “Orphan” GM Specialty and Small Market Crops?*, February 18, 2011, in Washington, DC, and by the Specialty Crop Regulatory Assistance (SCRA) initiative, *Nuts and Bolts of US Regulatory Dossiers for Genetically Engineered Crops*, December 6–8, 2011, in Riverdale, MD. A unique aspect of NABC 25 was the objective to formulate strategies to encourage progression to commercialization of GE specialty crops by public-sector researchers.

The presentations at NABC 25 were grouped in five areas:

- Opportunities and Challenges for Specialty Crops
- Genetic Engineering and Specialty-Crop Improvement
- Case Studies
- The Regulatory Process and Technology Access
- Perspectives from Relevant Groups

There follows a selection of “Major Issues” that emerged from the presentations and from the Q&A sessions, and “Opportunities and Challenges for Specialty Crops,” *i.e.* a more comprehensive listing of considerations underpinning the state-of-the-art as it relates to GE specialty crops, the paucity of commercialization of GE specialty crops and how this situation may be improved. Also presented are issues that speakers and audience members stressed as important under the rubrics of “Genetic Engineering and Specialty-Crop Improvement,” “Case Studies,” and “The Regulatory Process and Technology Access.”

In short, this chapter provides a relatively brief summary of the conference proceedings.

MAJOR ISSUES

The Dearth of GE Specialty Crops Commercially Available in the United States

- Virus-resistant papaya.
- Virus-resistant squash.
- Insect resistant sweet corn.
- Virus-resistant plum.
- Herbicide-tolerant sugar beet.
- Violet carnation.

Only a Few GE Specialty Crops Are Within the US Regulatory Process²

- Innate™ potato with reduced black-spot bruising and reduced asparagine content.
- Orange resistant to citrus-greening bacterial disease.
- Non-browning Arctic apple.

Barriers to Commercialization of GE Specialty Crops

- Current, time-consuming, costly, federal regulatory strictures.
- Uncertainty over the cost of achieving commercialization.
 - One report indicated that the cost of discovery, development and authorization of a new GE trait introduced to a commodity crop by a large company between 2008 and 2012 was \$136 million, of which achieving deregulation cost 26 percent (\$35.1 million) (Crop Life, 2011).
- Lack of access to essential technologies.
- Lack of interest on the part of major companies.
- Declining entrepreneurial spirit on the part of public-sector scientists.
- Declining funding for public-sector research.
- Need to invigorate public interest in new specialty crops advantageous to producers, to processors and to consumers.

Key Recommendations for Achieving Timely Deregulation and Market Acceptance

- Communicate with the appropriate federal agency/agencies early and often.
- Invest in the services of consultants to help negotiate the regulatory process.
- Non-GE identification of product, *e.g.* Innate™ potatoes and Arctic apples.

OPPORTUNITIES AND CHALLENGES FOR SPECIALTY CROPS

- NABC should organize an educational campaign for biotechnology, in particular *vis-à-vis* specialty crops. It is clear that the general public has negative feelings about foods containing genetically engineered (GE) ingredients because of “anti” campaigns.

²Not necessarily exhaustive.

- A positive marketing plan is needed, concentrating effort on sharing the science about specialty crops and combating negative messages.
- To reach the people influenced by activists, social media must be engaged.
- Industry needs a PR campaign in mainstream and social media to prove and publicize the benefits of biotechnology to health, the economy, and environmental and population trends.
- The orange juice/citrus-greening story should be used by industry to demonstrate that biotechnology is not only safe and economical, but essential for solution of special issues in agriculture.
- Although significant progress has been made by researchers in the public sector in terms of improving resistance of specialty crops to fungi, bacteria, insects and parasites, including parasitic nematodes, commercialization of GE specialty crops has been limited.
- Biotechnology can reduce the use of agrichemicals on fruits and vegetables, improve quality and yields, reduce post-harvest losses, enhance climate resilience, and increase nutrient value and economic returns. Good examples are the purple tomato³, which has high levels of anthocyanins, increased tolerance of disease and strong post-harvest stability, and potato varieties resistant to early blight⁴.
- The question is, *Will the potential for application to specialty crops be realized?* Given all of the good work that has been done, what's stopping it? Why isn't it moving forward? The stumbling blocks are not technical, but regulatory, non-access to essential technology, and social.
- Our universities are less involved in product development than historically. Lack of innovation and entrepreneurship in our public institutions—upon which to build new enterprises and refresh established products—has led to a weak pipeline of new technologies.
- Fewer than six public-sector transgenic crops have reached the market.
- A better way forward will not come from multinational companies due to lack of trust.
- The key challenges remain around achieving deregulation of traits and genes and in accessing technologies resulting from industry investments in first-generation GE crops. Opportunities will arise as patents expire.
- It would make sense to deregulate *Agrobacterium*-mediated transformation and at least some *Bt* genes, including those conferring resistance to Roundup and other herbicides. Similarly pathogen-derived resistance to viruses should be deregulated. We ought to be pushing APHIS and EPA for their deregulation more actively than we are.

³Developed in the UK.

⁴Developed in the UK and the Netherlands.

- A significant barrier at the EPA is interpretation of definitions. Virus resistance is called a pesticide because it controls a pest. A standard disease-resistant trait is not called a pesticide, but a transgenic one, which essentially means that DNA is being classified as a pesticide. Also of concern is that genes used to affect climate resilience—drought tolerance and so forth—are classified broadly as growth regulators. Chemical growth regulators are regulated, therefore genetic growth regulators should be thusly regulated.
- The cost of achieving deregulation within country need not be exorbitant. Commercialization of virus-resistant papaya in Hawaii in the 1990s cost approximately \$1.5 million. A new virus-resistant *Phaseolus* bean cost \$3.5 million from the start to product delivery within Brazil. Obtaining deregulation globally is significantly more costly⁵.
- A significant challenge in North America is reduced investments in discovery research.
- Increases in investment in agricultural science in the BRIC⁶ nations is directly related to their increases in productivity. The United States and Canada are seeing flattened or reduced investment;⁷ we are not keeping up with our competitors. It may well be that the advantage will be taken in less economically advantaged countries than in ours.
- An additional problem is limited understanding of how to achieve customer acceptance of biotechnology, due to concerns over food and environmental safety and intellectual property rights. In fact, consumer concerns are growing, as indicated by the labeling initiatives by activists and organizations who recognize that an anti-GE stance is supportive of their fund-raising activities.
- Edamame is a good example of a small-acreage specialty use of soybean that USDA funds for exploitation in the United States through the Specialty Crop Research Initiative (SCRI). The SCRI is a potential source of funding for GE research on specialty crops⁶.
- Farmers are applying lower levels of pesticides and soil health is improving. As a result of these improvements, key environmental groups—World Wildlife Fund, Environmental Defense Fund, Natural Resources Defense Council, *etc.*—are supporting GE crops more strongly. Also, we have improved food safety as a result of reduced levels of mycotoxin—a carcinogen—in *Bt* corn.
- Intellectual property is not the obstacle that it used to be.

⁵ See page 15.

⁶ Brazil, Russia, India and China.

⁷ However, as mentioned in the preface, the Farm Bill—passed in February 2014, during the preparation of this chapter—has restored the Specialty Crop Research Initiative funding, to about \$80 million per year. We are pleased with this reemphasis of the fundamental importance of research in specialty crops, consistent with the focus of this conference.

- Approximately 1 percent of the American public—including educated people—actually eat the amounts of fruits and vegetables recommended by the USDA.

GENETIC ENGINEERING AND SPECIALTY-CROP IMPROVEMENT

- We can transform virtually any plant with any piece of DNA, or RNA for that matter.
- In May of 1998, just 6 years to the day after ring-spot virus was discovered in papaya in Puna, resistant seed was released to growers. If research had been initiated after the virus had reached Puna there would be no papaya industry in Hawaii today.
- In Hawaii, non-transgenic and transgenic papaya have been grown for more than a decade, because Japan, until recently, imported only non-transgenic papaya. This was achieved using identity-preservation protocols.
- Deregulation of GE papaya in Canada was rapid because they acted on information from the United States.
- Due to politics and lobbying of activists, transgenic papaya will never be available to the Thai consumer and serious damage from the virus will continue to affect production and compromise the living standards of those who are most vulnerable.
- Transgenic papaya remains a public-sector anomaly.
- In 2010, worldwide insecticide use on major crop groups cost \$10.6 billion. Some 45% of the value of insecticides used was applied to fruits and vegetables, *i.e.* specialty crops.
- Our track record with *Bt* vegetables has been poor. The first was *Bt* potato, commercialized in 1995 to control the Colorado potato beetle, a primary defoliator in North America and Europe, resistant to many insecticides, with control costs of \$140 to \$300 per acre. When *Bt* potato appeared—a Monsanto product—growers liked it. In the second year it doubled in sales, and in the third year it doubled again. However, by 2001, it had fallen by the wayside. There were biological reasons, business-management reasons, and social reasons for the demise of the *Bt* potato. Activists pressured major producers of french fries not to use *Bt* potatoes. A somewhat similar example is General Mills' recent decision not to use sugar from GE corn for its major Cheerio brands but to use it for their other brands, indicating that the motive is marketing-based rather than healthfulness-based. Most ironically, a new class of insecticides, the neonicotinoids, had become available in 1995. They controlled aphids and leafhoppers as well as Colorado potato beetle. One new science technology won over another.
- At Cornell, new technologies are being taken to developing countries. The eggplant fruit and shoot borer is a caterpillar that farmers “traditionally” try to

control by spraying a cocktail of organophosphates, carbamates and pyrethroids, each of which has some human toxicity. Sometimes 80 sprays are required on a crop that reaches maturity in 80 to 90 days.

— It has been estimated that Greenpeace spent \$100 million to derail *Bt* eggplant. The minister for the environment, the last gatekeeper for *Bt* eggplant in India, enacted a moratorium in 2011, which is where it now sits.

- *Bt* sweet corn in the United States is a more successful story. In 2008 (the most recent data) it had ~9% of the total fresh-market acreage.
- In a study in Philadelphia, people looked at the quality of sweet corn, the freshness and if it was labeled “genetically engineered; they really didn’t care. Quality was more important than how it was produced.
- In 2011, Monsanto came out with a two-*Bt*-gene version of its ‘Obsession’ sweet corn, which was field-tested in comparison with its non-*Bt* counterpart. Yields were compared after spraying either zero, four, or eight times with the insecticide “Warrior.” Without *Bt* and insecticide, only 6% of ears were marketable. Even after spraying eight times, only 18% of ears were marketable. ‘Obsession’ with two *Bt* proteins produced 99% to 100% marketable ears, even without insecticide. Impressive!
- In Brazil, Embrapa⁸ scientists are producing a virus-resistant common bean (*Phaseolus vulgaris*). They expect it to be commercialized in 2014 or 2015, since the Brazilian government has the political will and they have scientists like Dennis Gonsalves with the passion to carry things through.
- An NABC survey of six land-grant universities⁹ revealed twenty six instances¹⁰ of genetic engineering of ten specialty crops¹¹; deregulation had been applied for in only two instances.
- Perhaps broad acceptance will occur first in developing countries where food security issues are most acute. Technology may be developed in the United State, go out to developing countries, and then come back.
- We need political will; we need scientific evidence; and we need social infrastructure with which to create policies that will foster the adoption of GE specialty crops.
- Consumers show little concern related specifically to GE specialty crops. Most objections are generic, *i.e.* to genetic engineering in general, rather than to GE fruits, vegetable, *etc.*, in particular
 - Some consumers view GE crops as potential “contaminants” of organic and even conventional crops.

⁸Equivalent to USDA-ARS.

⁹In Colorado, Illinois, Michigan, Missouri, New York and North Carolina.

¹⁰Fire-blight resistance, cold tolerance, early flowering, herbicide tolerance, bacterial resistance, insect resistance, vaccine synthesis, anti-cancer agent synthesis, *etc.*

¹¹Apple, blueberry, brassica, celery, cherry, citrus, grape, peanut, potato and tomato.

- The demand for mandatory labeling of foods containing GE ingredients is gathering momentum. Much of the underpinning discussion revolves around the issue of “right to know.” On the other hand, pro-labeling referenda recently failed in California and Washington State.
- A first requirement is comprehensive federal regulation and oversight that ensures consumers that GE crops are safe to eat and do not adversely affect the environment.
- In 1992, a voluntary consultation process was established by the FDA on the basis that GE crops are “substantially equivalent” to their conventional counterparts. To date, all those who have commercialized GE crops have complied with voluntary consultation. However, this voluntary process is not sufficiently comprehensive. In the late 1990s, NABC recommended that this process be required, not voluntary, and in 2004, Senator Durbin introduced the Genetically Engineered Foods Act, which would mandate the consultation process without changing the safety standard or the data requirements. The FDA would provide formal certifications of safety. It would not lengthen the process but it would give consumers confidence in the federal government’s oversight.
- The USDA needs to monitor stewardship more comprehensively. There is evidence of resistance to *Bt* in corn rootworm and of herbicide-tolerance in weeds, possibly resulting from poor stewardship by farmers and by some biotech companies.
- There is need to anticipate and address issues that affect consumer acceptance of GE specialty crops. There is need to educate, inform and listen to the farmers and relevant farm organizations. There is need to listen to food-chain actors and to educate them, including grocery stores, as well the media.
- It is important to put in place segregation procedures to prevent commingling of GE and non-GE seed.
- Although transparency will improve consumer confidence, labeling of GE foods should not be mandatory. Strong, but not stifling—“appropriate”—regulations will reassure consumers.
- European plum, genetically engineered for resistance to plum-pox virus, was successfully registered by an ARS scientist. Clearly, the technologies are in place and the regulatory system can work, opening the way to deregulation of other GE specialty crops.
- There will be no “hall pass” for devising more precise ways to produce new genotypes. Activists are likely to ask “Why don’t we just label that as GE food?” in spite of the fact that some eighty research papers have elucidated labeling’s negative impacts.
- Plant-breeding potential is ever-expanding, particularly with new genome maps, RNA silencing, zinc fingers, *etc.*

- Until you resolve manufacturing/retailer/consumer acceptance, you don't know if the process of achieving deregulation will be worth it,
- About 15 percent of the public definitely will not buy a GE fruit or vegetable in the marketplace.
- A blueberry-genome sequencing effort that will be completed by the end of summer 2013. It's a complicated genome that no one else wanted to tackle. The database will be open to people looking at cranberry and other plants in the genus *Vaccinium*. Knowing the genomics will lead to understanding beneficial activities within the human body.
- The launch of the Plant Pathways Elucidation Project ("P-Squared EP") is planned for June 2013. North Carolina State and the University of North Carolina-Charlotte will be academic partners. NC State will handle the biology whereas Charlotte will handle bioinformatics; the biological data will go into a knowledge-based cloud over the whole project to feed information into what a plant makes, how it makes it, what's the pathway it takes to get there, and what good the product is for human health. In building this knowledge base, Dole and General Mills will be industry partners and Castle & Cooke will be a sponsor. Developed technologies will aid understanding of how specialty crops contribute to human health.
- General Mills and Dole have opened their files on pathways they have elucidated for oat, pineapple, and berries, and they are looking to university researchers to pull together teams for analyses of complex pathway analyses. Early efforts will focus on four crops: oat, broccoli, strawberry and blueberry.
- A need exists to use synthetic genomics to take beneficial traits that have utility under specialized conditions and combine them with photosynthetic efficiency, to carbon to be channeled to target molecules and show improved tolerance of environmental stresses. One of the most important research areas is improvement of photosynthetic efficiency.

CASE STUDIES

Citrus Greening

- The infection rate of citrus greening—discovered first in 2005 in Florida—is now 100% of Florida groves.
- Initial replanting efforts resulted in high levels of infection in less than five years.
- The solution to the disease, will involve four concurrent processes:
 - Research
 - Regulatory approval
 - Horticultural/agricultural production
 - Consumer approval.

- The major focus of the research is at Texas A&M, on the development of a disease-resistant tree through genetic engineering. Two genes that confer resistance are being transferred to citrus from spinach.
- Accordingly, the solution will involve a plant-incorporated protectant (PIP). Tests required by EPA, USDA and FDA are projected to cost in excess of \$3 million, including the cost of three law firms in Washington, DC.
- Since genetic engineering will be involved, education will be fundamental to gaining consumer acceptance.
- The first most important benefit is that the orange juice industry will survive in the United States.
 - Another major benefit will be the elimination of the insecticides now being used in large amounts to control the insect vector.
- At the current rate of progress, resistant trees will not be commercialized until 2019. Effort is focused on accelerating the process.

Non-Browning Apple

- The Arctic apple has no polyphenol oxidase, the enzyme that drives the browning reaction.
 - Non-browning can be achieved with any variety.
 - RNAi is used to silence the four genes that encode polyphenol oxidase.
- Growers interested in planting Arctic apples will have to agree to apply a sticker to each fruit. It doesn't say "genetically engineered," but it does say "Arctic."
- Achieving deregulation is doable and is not exceedingly expensive. People shouldn't be thinking in terms of millions of dollars. The out-of-pocket component isn't that much.
- Deregulation is expected in the United States and Canada by the end of 2013.
- The message to the consumer is short and sweet: it's just like any other apple; it looks like an apple; it grows like an apple; and it tastes like an apple. It just doesn't go brown.

Improved Potato

- J.R. Simplot's Innate™ brand provides a way to talk about genetic engineering without resorting to the less consumer-friendly terms, "intragenic" and "cisgenic."
 - Explanation of the Innate technology to consumers produced acceptance close to that of "plant breeding."
- The word "biotechnology" elicits greater comfort among consumers than "GMO."
- Traits being brought to market using "Innate 1.0" potato are reduced black-spot bruise, and reduced asparagine.
 - To achieve these improvements, one of the five or six polyphenol oxidase genes and the gene for asparagine synthase were silenced in a tuber-specific

manner. Instead of asparagine—a precursor of toxic, carcinogenic acrylamide—the modified tuber accumulates glutamine instead.

- Those whose job is to improve potatoes, and who are focusing on the farmer, are missing 80% of the potential. Downstream companies that make products from potatoes are the big sellers.
 - Farmers produce \$3.5 billion worth of potatoes every year, whereas somewhere around \$40 billion worth of French fries are sold.
- It can take a while to structure relationships and induce consumer comfort with biotech. On the other hand, after they're comfortable, support can be significant. Of 80 comments received—solicited by APHIS—25 have been positive, many from growers.

Vegetables

- Monsanto's major play in vegetables is to take advantage of advanced breeding techniques, which entail the ability to associate, at the genetic level, from a trait perspective back to a molecular marker, which allows breeders to be more efficient in making selections.
- Thousands of markers have been identified in vegetable crops. Yearly throughput of marker-based data points has increased 100-fold since acquisition of Seminis in 2005.
- Once the donor source of resistance is identified, the marker for the trait can be identified and introgressed into any number of plant types: success has been achieved in producing mildew-resistant cucumber, *Phytophthora*-resistant peppers and virus-resistant squash.

THE REGULATORY PROCESS AND TECHNOLOGY ACCESS

- FIFRA is unusual in that it considers benefits, but it can apply to plant-incorporated protectants (PIPs) in terms of environmental safety and benefits and even economic safety and benefits.
- Experimental Use Permits (EUPs) are issued by EPA to facilitate the generation of information or data necessary to register PIPs.
- FIFRA dictates that cumulative terrestrial trials of >10 acres (4 ha) or aquatic trials of >1 acre per year per PIP require EPA approval via experiment use permits (EUPs).
- EUPs are time limited and require reporting of results, including adverse events.
- Petitions to APHIS involve two evaluations:
 - Risk assessment—as a stipulation of the Plant Protection Act—to answer the question: *Does the genetically engineered organism pose a plant-pest risk?*
 - Environmental assessment—as a stipulation of the National Environmental Policy Act (NEPA).

- APHIS-BRS has made determinations of non-regulated status in response to over 90 petitions, comprising 16 plant species.
- In 2011, a memorandum was issued by the White House Office of Science and Technology Policy in conjunction with the Office of Management and Budget and the US Trade Representative's Office—frequently referred to as the Holdren memo—titled *Principles for Regulation and Oversight of Emerging Technologies*. Although it is not aimed at biotechnology alone, it is similar in tone and emphasis to the *Coordinated Framework for Regulation of Biotechnology*, *i.e.* favoring innovation, having enough regulation as necessary and to consider that there may be no need for regulation.
- The Sanitary and Phytosanitary Agreement under the WTO, which came into being in 1995 says, in essence: “In the absence of good scientific evidence that demonstrates harm to plants, animals or to humans, we should not restrict trade.”
- The Food and Drug Administration (FDA) cannot make consultation mandatory, because no law permits it.
- FDA has a program to help developers ensure that food from new plant varieties is safe and complies with regulations. Three legal requirements are applicable.
 - Safety: The food is as safe as that generated from traditionally bred varieties.
 - Labeling: The labeling is truthful and not misleading.”
 - Additives: Is premarket review required?
- Submissions to FDA are evaluated by two centers for different uses:
 - Safety of use in human food is evaluated by the Center for Food Safety and Applied Nutrition (CFSAN).
 - The Center for Veterinary Medicine (CVM) evaluates safety of use in animal feed.
- A new protein that is neither toxic nor allergenic is considered safe for field testing and FDA will not be concerned if low levels appear inadvertently in the marketplace.
- As science evolves, new technologies and traits will appear. However, FDA expects that the policy developed in 1992 will be sufficiently flexible and broad to accommodate them.
- Canada differs from the United States in that it regulates novelty: novel feed, novel food and novel plants.
- The Canadian focus is on the product, not on the process used to develop that product. Accordingly, a regulated product can be developed by any breeding process—including conventional breeding, genetic engineering or mutagenesis—and this approach allows the Canadian regulatory system to efficiently adjust to any new developments in science or plant breeding.
- The main sources of concern expressed by members of the public are adverse effects on honeybees and monarch butterflies.

- Resistance-management programs are monitored to determine levels of compliance.
- Specialty crops account for less than one-tenth of one percent of the 420 million acres of GE crops produced in the world today.
- The comprehensive—if somewhat complicated—regulatory system in the United States has worked fairly well since the mid-1980s, although it may be argued that improvements are now needed.
- Approval times for genetically engineered crops have ballooned from approximately 6 months to over 3 years.
- Much has been said about the high cost of achieving regulatory approval for GE-crop traits. Published numbers have ranged from \$6 million to \$15 million for global approval. A recent study quoted \$35 million—even up to \$150 million—for global approval of commodity crops.
- The concept of a talent agent is relevant. In contrast, researchers don't have agents; they are on their own.
- Scientists should be encouraged to look for opportunities to transfer their research vision into results that may change the world.
- The Public Intellectual Property Resource for Agriculture (PIPRA¹²) was formed by the Rockefeller Foundation.
- PIPRA freedom-to-operate assessments for public-sector projects to determine if products or processes use third-party proprietary technologies and, if so, can the project obtain the rights to those properties? PIPRA also looks at materials used and material-transfer agreements, which are always the more problematic.
- The Specialty Crop Regulatory Assistance (SCRA) program was set up in 2004, under the auspices of which have been held several meetings, mostly workshops that have included developers of GE specialty crops and representatives of the regulatory agencies.
- How much in addition has to be spent to generate the additional data required by regulatory agencies for appraisal of a GE trait? When you do those calculations, the marginal cost comes down to the order of a few tens of thousands of dollars.
- Talking directly to the regulators is the best way to find out what information and data are actually needed.
- Attempts continue to secure long-term funding to maintain SCRA functions, including meetings and direct and indirect assistance to GE specialty-crop developers.

¹²PIPRA enables access to public innovation. PIPRA supports innovation in agriculture, health, water, and energy technologies. In collaboration with 50+ universities and research centers and a pro bono attorney network, PIPRA provides intellectual property rights and commercialization-strategy services to increase the impact of public-sector innovation, particularly for developing countries and specialty markets.

- Gaining deregulation is still the major stumbling block to the commercialization of GE specialty crops.
- There's a need to address a range of traits, for which genetic technologies are the best tools in the toolbox. This implies the need to overcome public resistance and the need to overcome misperceptions about the onerousness of the regulatory system.

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PART II—KEYNOTE PRESENTATION

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Opportunities and Challenges for Specialty Crops: Will They Sell If Developed?

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With this presentation, my role is to help to stir the discussion. Perhaps it will open the dialogue so that we have a sense of where we have been, where we are, and then what's ahead. Figure 1 shows a photograph from 1986, and in Figure 2 is a photograph taken two years later. We developed a tomato phenotype—viral coat-protein-mediated resistance to a common disease of tomato—with a technology that we hoped would be applicable to other horticultural and agricultural crops.



Figure 1. 1985: Coat-protein-mediated resistance to virus infection in tomato.

Since the field trial, fewer than six public-sector transgenic crops have reached the market in the United States. For the last 15 or 18 years, we've asked why it's been that way and if the situation will improve in the near future. If it does get better, what steps will be required to get there. I will discuss this in the context of reduction of the use of



Figure 2. 1987: First field trial of genetically modified tomato plants similar to those described in Figure 1, conducted in Jerseyville, Illinois.

pesticides and improved sustainability, and the role that this and other sciences play in the economy.

Increasingly, the topic of this conference, biotechnology and horticultural crops, is about the ability of producers to make a profit, and how future agriculture, globally, will include specialty crops. Although we cannot accurately predict the future of technical successes or consumer acceptance of new crop varieties, we should be planning ahead, as it can take 10 or more years to bring a new technology to the market. We should be looking ahead at what the economic picture may be—knowing what farming is like today, knowing what smallholders in Africa might want, or what might be useful in the prairies of western Canada, in Florida and other regions of the world.

I want to consider the technical opportunities and market challenges and possible solutions in the biotechnology of specialty crops, and then look for trends and goals that may portend a brighter future. We know where we've been. The technologies that were developed in the 1980s in transgenesis provided good products that brought value to producers and, arguably, to consumers by keeping food available at reasonable cost; also, they brought environmental benefits.

However, progress in applying the new technologies to specialty crops has been limited. The stumbling blocks are not technical, but regulatory and social. The challenges are magnified by the fact that the crops are of relatively small acreage and that consumer concerns over genetically modified (GM) crops are not waning. Activists are becoming more vocal, and we don't seem to have a plan for mitigation of damage that they cause to the effort to develop useful varieties through biotechnology. Nevertheless, public-sector scientists have continued their investment in the technology as it fits their research goals, and they continue to create products that are likely to have value, should they be adopted. As a plant pathologist, it is heartening to see the progress that has been made by researchers in the public sector, for example improving resistance to fungi, bacteria,

insects and parasites, including parasitic nematodes, in specialty crops. Virus-resistant traits have been introduced in many specialty crops.

Biotechnology has also been employed to enhance nutrient content in tomato, rice, maize and other crops. Good examples are the purple tomato with high levels of carotenoids, increased tolerance of disease and strong post-harvest stability, vitamin-C-rich carrot, and potato varieties resistant to early blight and to late blight. A large number of virus-resistant crops have been developed by researchers abroad, showing how science and biotechnology have proven to be valuable. The question is, Will the full potential for application to specialty crops be realized? Given all of the good work that has been done, what's stopping it? Why isn't it moving forward? It is not a technical problem. Clearly, other issues need to be addressed.

A LONG-TERM VIEW IS NECESSARY

Let's look at today's problems in the context of what the long-term future might bring in agriculture, and ask several questions for US agriculture:

- Who is defining the long-term future of US agriculture in competition with BRIC¹ nations and other emerging economies, and how will decisions in technology and markets impact the future?
 - What will be the impact on US agriculture of increased productivity of commodity crops in Eastern Europe and South America?
 - Over what timeframe will changes occur?
- In the context of: increasing focus on health and nutrition, how will technology in horticultural crops be judged? How will value added to agricultural products be captured and will it change? What will be the impact of ongoing changes, both positive and negative, on farm economies in an era of high land values? And how will land values' impact on the roles of specialty versus commodity crops in the US economy change?
- What will be the markets for US agriculture exports when African nations become food self-sufficient in 20 or 25 years (as some have predicted), and when/if Eastern Europe produces more wheat and corn for European markets, and when Brazil fully exploits the Cerrado² for production of increasing amounts of soybean and corn?

If you ask who is in charge of outlining a plan for America's agricultural future, you may not find a long-term plan, though a mid-term roadmap was developed by the USDA in 2012. A useful roadmap should identify and address the challenges to the future of America's agriculture. Are increases in yields possible in commodity agriculture and what is required to achieve yield goals? What will impact the future profitability of specialty crops and how will challenges be managed? At the end of the day, a major issue is whether

¹Brazil, Russia, India and China.

²A vast tropical savanna, the largest of Brazil's major habitat types after Amazonia.

or not the farmer/producer can make a living, whether (s)he can still pay the mortgage on the land and purchase the equipment that will affect profitability, and contribute to the wellbeing of the family. A useful roadmap will plan forward to provide a basis for ongoing success in the industry.

In a recent publication—*Agricultural Innovation: The United States in a Changing Global Reality*—Philip Pardey and Jason Beddow (2013) enumerated future challenges to agricultural economics that can be useful. We in the sciences and business sector, focused as we are on our own projects and products, often forget the bigger picture, to our detriment. To capture new value from agricultural products, there's an increasing awareness of the potential value of a growing bioeconomy and of biorefineries. Similarly, the growing role of consumer preferences and demands for agro-sustainability will continue to change agriculture. For example, I am convinced that biotechnology can reduce the use of agrichemicals on fruits and vegetables, improve quality and yields, reduce post-harvest losses, enhance climate resilience, and increase nutrient value and economic returns. If I am correct, investments made in research that helps to achieve these goals will prove to be warranted. The risk is that I am incorrect and that consumers will not push to reduce agrichemicals. To increase the likelihood that sound research goals are set, it will be helpful to engage the broad range of skills from the social sciences—including economics, consumer studies and policymaking—in the goal-setting process.

THE RIGHT TECHNOLOGIES AT THE RIGHT TIME

Recent advances in the science and technology of molecular plant breeding make it possible to consider the future of applications of biotechnology to horticultural and specialty crops that may be brought forward, for example new energy crops and those that produce biopolymers for the rubber and plastics industries. Quality of product and quantity of production can now be advanced rapidly by modern breeding and used to improve resilience to climate change and extreme weather, and to increase fertilizer-use efficiency. Furthermore, previously unexploited specialty crops may be employed for new industrial uses by applications of synthetic biology to alter metabolism and create useful products. Tools available today are far more powerful and useful than what we used, or imagined, in 1985 when we developed the first virus-resistant tomato plants. New tools include:

- High-frequency mutagenesis to create variability and select desired changes in target gene(s)
- Directed nucleotide changes in target genes to recapitulate known/desired variations
- Site-specific gene insertion
- Artificial chromosomes to carry multiple genes
- Deletion/inactivation of non-desired gene(s) via meganucleases
- Non-transgenic progeny via segregation in breeding
- Gene inactivation by RNAi-based approaches, including directed methylation and knockout.

We can expect continued technical improvements of course, and some of the new technologies will push the relevant regulatory processes to consider advantages of enabling technologies as well as the products to which they lead. The objective of the new technologies is not to circumvent regulatory oversight, but to develop new materials that will have increased value for those who take them to the marketplace and to the consumers who will use them.

OPPORTUNITIES AS PATENTS EXPIRE

New opportunities for development will come through the expiration of patents and will lead the way to generic products, or will release constraints on commercial development of new products. Although patent protection for *Agrobacterium*-mediated transformation of plants will not expire until the late 2020s, products that made use of the technology will become generic much sooner. For example, the coat-protein gene-based virus-resistance patent was issued (17 years after filing) in 2003, and will be generic by 2020.

Certain technologies for Roundup resistance, and for insect resistance will likewise expire in the early 2020s and lead to new opportunities for new applications.

CHALLENGES AND THREATS

The key challenges to development of biotechnology products in specialty and horticultural crops remain around the cost of regulation of traits and in accessing technologies resulting from industry investments in first-generation GM crops. We look forward to having not only resistances to disease and insects that were developed in first-generation crops, but also we look forward to herbicide tolerance and other traits that will come off-patent in the next 5 to 10 years.

Many relevant and valuable traits have been demonstrated in specialty crops, but few have been introduced in the marketplace. As others have reported, the significant cost of deregulating a biotechnology product compared with the value of the trait per se is a real and ongoing problem, especially in those cases when a disease or insect pest affects a relatively small geographical area.

In other cases, there is lack of scientific and technical information to bring to bear on a problem. A significant challenge in North America—as relevant in Canada as in the United States—is reduced investment in discovery research. We all ought to be concerned about this. Pardey and Beddow (2013) noted that increases in investment in agricultural science in the BRIC nations is directly related to increases in their crop productivity. In contrast, in North America there is flattened or reduced investment in research in agriculture-related sciences in inflation-adjusted terms; we are not keeping up with our competitors, although we have built successful agriculture economies on such competition. In 2012, the United States exported nearly \$140 billion worth of agricultural products. Yet, in the United States, the Department of Agriculture invests less than \$2.5 billion dollars annually in research, and less than \$350 million dollars is available for competitive research grants. That level of investment is catching up with us, begging the question of agricultural profitability in the continent in 20 to 50 years. The negative impact of less discovery research could be substantial.

The weak history of innovation and entrepreneurship in our public institutions, upon which to build new enterprises and refresh established products, has led to a weak pipeline of new technologies. I participate as an advisor on several venture-capital funds and the paucity of innovation has, to date, been noticeable and is significantly less dynamic than from the biomedical community, and far less than for the IT sector.

It's not that the science itself is not outstanding. It is common to hear venture-fund managers reflect on the lack of innovation in this market sector and to relate it to the fact that the way to market for products improved by certain genetic technologies is unclear. The weak pipeline of new technologies, and the heavy and high-cost regulatory process in the United States and globally causes delays in release of new products. This is confounded by the lack of harmonized and synchronous approval processes that have together slowed product approval, which, in turn, has slowed innovation. This is further exacerbated by the weak acceptance of new products by a very vocal minority of consumers—in particular products developed by multinational corporations—which affects all of us.

These are some of the significant threats and challenges that affect the applications of biotechnology to horticultural and specialty crops. On the upside, the USDA process has improved modestly. There are additional requirements, but maybe we should have predicted some of the changes, for example the growing need for studies of environmental impact of new products, as unscientific as it may seem in some cases. Maybe we should have expected the changes. EPA and the NEPA³ rules continue to represent substantial barriers to the release of new products.

The global approval process—which negatively impacts release of new products here in the United States—continues to be slowed by a variety of factors. And then there are events like the GM wheat that appeared recently in Oregon, and you wonder how long that tale will last, and how it will be used and by which group. Careful investigation is needed to elucidate how that happened in order to prevent recurrence, whether by accident or by intention.

Consumer concerns around GM crops are no lower than they were a decade ago, and are growing in some regions, as indicated by the labeling initiatives that we see in as many as 20 states. The same issues apply in Canada and in countries around the globe: we as scientists have a lot of work ahead as we take a more active role in discussions about GM foods.

DEREGULATION OF PROVEN TECHNOLOGIES

Many scientists, though not all, are convinced that some of the controversies around GM food would diminish (1) if the benefits of GM varieties were more apparent to the consumer, and (2) if regulatory hurdles were reduced to levels commensurate with risk. It would help if agencies would deregulate based on past experience with a technology, and based on scientific evidence of no or minimum risk. At the same time, this would demonstrate to the public that—while the regulators are watching carefully—this is not

³National Environmental Policy Act.

a dangerous technology. We have boxed ourselves *in vis-à-vis* consumers by saying that the technology needs lots of regulation, when, in fact, most in the science community recognizes that it does not. Many feel that it is logical to deregulate *Agrobacterium*-mediated transformation, at least some Bt genes, and genes that confer resistance to herbicides proven to be effective and safe for the environment. Similarly, pathogen-derived resistance to viruses should be deregulated. Also, I would include all RNAi approaches to control pathogens, in particular when siRNAs are shown to be part of an innate defense mechanism. However, I am not optimistic that this will happen in the near future. But, since we have 20 to 25 years of success with some technologies, we ought to be pushing APHIS and EPA to deregulate certain technologies more actively than we are. And if APHIS is, as they claim, a science-based regulatory agency, we should expect to receive informed responses. This may be a way that we in the academic community could help to move beyond the current slow-and-go regulatory process and move new products to market more rapidly than they are today.

PERCEPTION OF MULTINATIONAL COMPANIES

I am convinced that many of the challenges that we in the public sector face in our difficulties in GM agriculture are because many of us in university research are not seen as relevant to local agriculture *per se*. It is not easy for consumers of food to connect with our laboratory research. Instead, they generally see agriculture and the food economy as connected to large agribusiness and multinational food companies, which, they are convinced, do not have consumers' interests at heart. Although we know that not to be the case, we academics are either not seen as relevant or are painted with the same brush.

For some time, I have had a sense that this issue has arisen because our universities are now less involved in product development than historically. One way to minimize the latter may be for regulatory agencies to deregulate essential technologies that are broadly applicable, so that we can use them to address local problems. Horticultural and specialty crops are regional in their relevance. In the mid-1990s, Benigno Villalón who developed thousands of varieties of hot chili peppers in Texas, sent a postdoc to my lab to develop coat-protein resistance to viruses, which commonly infect chili peppers. However, he withdrew the effort on realizing what would be involved in achieving deregulation. Similarly, there is much innate interest in using genetic engineering to tackle local pest and disease problems in many crops.

ACHIEVING DEREGULATION

New technologies are developed in public research institutions as well as in small and large privately held companies. The deregulation process as it currently stands is poorly defined and costly. Achieving deregulation of virus-resistant papaya, led by Dennis Gonsalves⁴ of the USDA in Hawaii is estimated to have cost less than \$1 million. In Brazil, a new virus-resistant *Phaseolus* bean cost \$3.5 million from the start of the project to product

⁴Pages 37–46.

delivery. On the other hand, putting a new trait into a globally important crop—maize, soybean or cotton—is expensive, estimated to be between \$50 million and \$150 million, depending upon what is required. This discourages innovation, and it certainly discourages venture capitalists from investing in projects to which they cannot predict an end-point. In some ways we don't have a discovery problem in certain technologies, but we do have an innovation and translation problem. Policymakers are reluctant to develop long-term policies for the agriculture/food sector, including regulatory policies for new technologies.

An additional problem is limited understanding of how to achieve customer acceptance of biotechnology, due to concerns over food and environmental safety and intellectual property rights. The past 20 years haven't worked well for us, yet we have little concept of what we should be doing. A better way forward is not likely to come from multinational companies due to lack of trust on the part of consumers. But unless we face this impasse and find a better way, in 10 years we will still be asking ourselves, "Why isn't there more acceptance of crops developed with new genetic technologies?"

MESSAGING AGBIOTECH FOR PUBLIC CONSUMPTION

In 2011, Graham Brookes and Peter Barfoot published a paper titled *GM Crops: Global Socio-Economic and Environmental Impacts 1996–2009*, which focused on positive economic impacts, and production and environmental effects of GM crops. Within a week of the publication of Brookes and Barfoot (2011), Vandana Shiva and colleagues (2011) published *The GMO Emperor Has No Clothes: A Global Citizens [sic] Report on the State of GMOs—False Promises, Failed Technologies* (Figure 3). Certainly this was no coincidence.

At an NABC conference some years ago, I remember standing and asking her, following her remarks to the attendees, "Do you really teach this to your students? Do you call yourself a scientist? Do you really believe what you are saying?" My questions didn't matter, of course. Vandana Shiva has been saying the same things, making the same accusations, for the last 15 years, and because this is the kind of "stuff" that garners publicity, the issue won't go away. The private sector has yet to learn how to message agriculture and biotechnology for public consumption and how to address those who attack their work unrelentingly.

What might be done to counter? In my opinion, we should encourage transparency at all stages of the process—from research to testing, to product development and regulatory approval. Perhaps we should "open all the books"; perhaps that would help. And, there should be more public-sector voices in support of science and technologies in food and agriculture. And, in terms of transparency in our work, we need to demonstrate that we are, in fact, looking at real advantages, real sustainability, with real reductions in the use of agrochemicals, and other important outcomes for the research that we are engaged in.

MEETING GLOBAL FOOD SECURITY.

What we do in specialty crops is part of the challenge of meeting global food and nutrition security. According to the FAO, we must feed another 2 billion people with sufficient

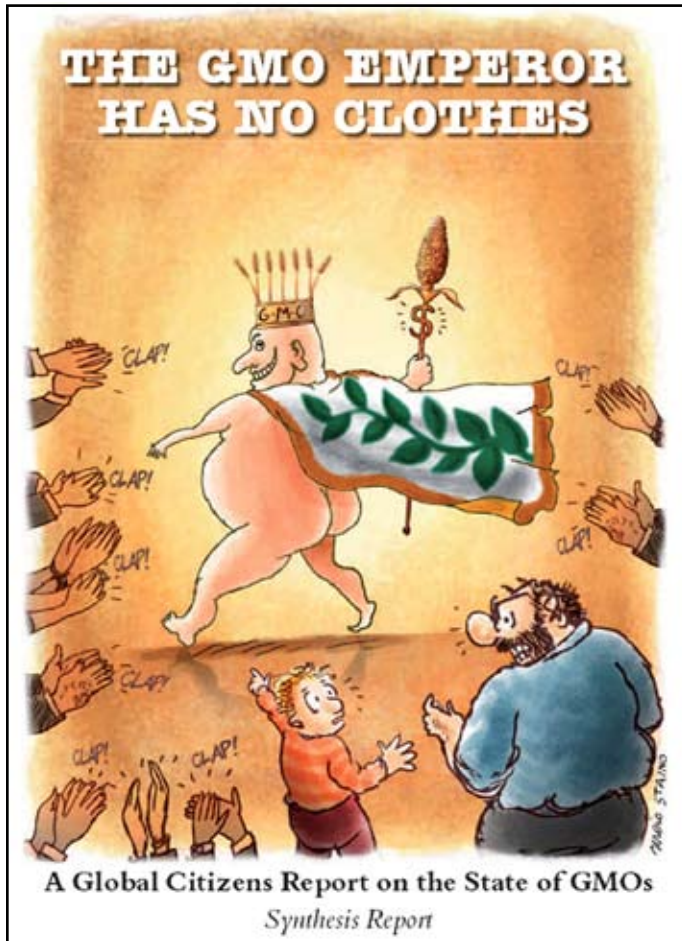


Figure 3. 2011 report by Vandana Shiva *et al.*

calories and nutrition, from a safe food supply, at acceptable cost, from the same area (perhaps up to 10% more) of arable land. This will have to be achieved with less water, and smaller inputs of fertilizer and other chemicals. Again according to the FAO, the foreseeable future will require a 70% increase in food production, a 43% increase in grain production, and a 75% increase in meat production. Specialty crops are part of the solution, in terms of producer economics as well as part of the solution in nutrition, health, and wellbeing of the consumer.

If what we are doing really does matter, the question is: can we broaden the use of advanced science and technologies to include horticultural and specialty crops?

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ROGER BEACHY is the founding executive director of the newly established World Food Center at University of California, Davis; in 2013 he served as the Executive Director of the Global Institute for Food Security at the University of Saskatchewan in Saskatoon, SK, Canada. He is also president emeritus of the

Donald Danforth Plant Science Center, and was the first director of the National Institute of Food and Agriculture (NIFA). Prior to this appointment, he served as the founding president of the Danforth Center.

From 1991 to 1998, he headed the Division of Plant Biology at the Scripps Research Institute. He was also professor and Scripps Family Chair in Cell Biology and co-director of the International Laboratory for Tropical Agricultural Biotechnology at Scripps. From 1978 to 1991, he was a member of the Biology Department at Washington University in St. Louis, where he was professor and director of the Center for Plant Science and Biotechnology. His research has produced more than 230 journal publications in virology and virus pathology, and regulation of gene expression in plants.

Dr. Beachy is a member of the US National Academy of Sciences and in 2001 received the Wolf Prize in Agriculture. He is a fellow in the American Association for the Advancement of Science, the American Academy of Microbiology, the National Academy of Science India, the Indian National Science Academy, and the Academy of Science of St. Louis.

He holds a PhD in plant pathology from Michigan State University and a BA in biology from Goshen College.

Opportunities and Challenges for Specialty Crops: Will They Sell If Developed?

Q&A

MODERATOR: DAN LINEBERGER

*Texas A&M University
College Station, Texas*

Andrea Fonseca (Texas A&M University, College Station): You said that multinationals won't work. Can you elaborate on that?

Roger Beachy: My point is that the multinational companies, who are the most successful in the science and technology and in product development in GM agriculture, are heavily criticized for the appearance that they are "taking over the world's germplasm and will control farmers." So, while what the report about the safety of GM foods has been scientifically validated, the multinationals are tainted in the eyes of some consumers. My colleague at Washington University, Professor Garland Allen, a historian of science said, "Roger I have a plan to make food available for free for everybody in the world." While some may feel that government should take on this role, others of us believe that the private sector plays an important role in food and agriculture.

Fonseca: Okay, I see what you mean.

Beachy: And he's not alone. That was my context.

Fonseca: You mentioned EPA barriers. What, in your opinion, is the most significant barrier at the EPA?

Beachy: The interpretation of definitions. For example, virus resistance was referred to as a pesticide because it controls a pest. In contrast, conventional disease-resistant traits are not called pesticidal. Describing a transgenic trait as such implies that DNA, or in some case RNA, is being classified as a pesticide. Another one that concerns me is that

genes used to affect climate resilience—drought tolerance and so forth—are classified broadly by one agency as growth regulators. The definition of a growth regulator in that context seems ridiculous. A learning should go on and the learning is called biology. It's called genetics. It's called plant physiology. It's called pathology. It's called information that we appreciate as science, and the consensus that results is what we know as scientific validation. Those are some of my concerns about the EPA. The need for regulation of GM crops of this type is something that I don't understand.

Nikhil Patil (Texas A&M AgrLife Research, College Station): You did a great job in presenting the whole perspective on local food security. We all know that we cannot achieve global food security without GMOs. In the early years, Europeans failed, in my opinion, to provide good education about GMOs. In the United States we are doing a little bit better in terms of educating people. Do you think we can improve global food security by inclusion of GMOs?

Beachy: We have a long way to go. We have yet to see Golden Rice in the market; it has been delayed for nearly 15 years. GM technologies are not yet considered part of the nutrition solution. We haven't yet seen *Bt* brinjal⁵ in the Philippines, Bangladesh, or India. In the early days, China released some GM peppers, cucumbers and tomatoes that were virus resistant. So we know it is possible to move products of public sector research to the marketplace. There are ongoing field trials in Uganda with a bacterium-resistant banana, and I think that there are disease-resistant banana, cassava and sweet potato in trials. And there is GM cowpea with resistance to bruchid beetles. It may well be that the advantage for use of GM-horticulture crops will occur more effectively in less economically advantaged countries than in ours. It doesn't sound very good for a specialty crops meeting like this one, but that may well be the way it will happen. Perhaps we need to think in terms of importing sweet-potato fries from Uganda made from GM plants.

Bob Avant (Texas A&M AgriLife Research, College Station): Recently USDA announced they were going to go through an EIS⁶ process for deregulation of GMOs using the NIFA⁷ process. Typically, environmental activists use that as a way to delay or kill projects. Do you think that doing EISs on GMOs will have a chilling effect on getting additional traits deregulated?

Beachy: I don't think it will if we do it right. We ought to take our medicine if that's the way it's going to go before the law is changed, if ever; perhaps we could include EIS-related studies with every field trial. Create the portfolio and just get it done. Of course, this requires that the EPA and USDA define adequately what an acceptable EIS is. We should learn the steps and collect the necessary data up front. That way, it won't cost the developer additional years and another few million dollars. Just do it.

⁵Eggplant/aubergine.

⁶Environmental impact statement.

⁷USDA's National Institute of Food and Agriculture.

Bill McCutchen (Texas A&M AgriLife Research, College Station): You've been through the genesis of this. What do you see as the path of least resistance for public institutions—land-grant universities—to actually get our transgenic specialty crops deregulated? You pointed out some facts, but why can't we come together and get it done?

Beachy: I don't know. Why can't you?

McCutchen: I don't know. That's why you're the keynote speaker.

Beachy: Something occurred recently that shocked me. At an annual meeting of the American Phytopathological Society, I gave a forward-looking speech and a number of students who gathered around afterward said they had been told by their professors not to consider GM approaches. We have to start in our universities by saying that GM technologies are part of plant breeding. Everybody in science should know about genetics and plant breeding, including genetic engineering, and their role in agriculture sustainability, food safety, nutrition, and so on. We've got to start with education. The other approach may well be to begin talking about our current crop-genetic-engineering research projects in a transparent way, so that when the results are in we can say, "This is what your investment has brought us." In the world of cancer research, they talk about solutions for many years before they accomplish them, which in a way justifies the continuing investments in cancer research, and why there is a cancer center at a hospital or in a university setting near you. In agriculture we are reluctant to describe our goals or that we might be using advanced genetics to achieve them. Perhaps there's a marketing point here that universities should pursue. Maybe it should be led by the APLU⁸. Maybe it should be led by science societies, by the groups of plant producers or plant breeders who come forward to say that this is a key part of the technology that will achieve drought tolerance or insect resistance or lower-glycemic-index rice that tastes like its high-glycemic-index counterpart. Whatever the goal, we should indicate it now and that we expect achievement in 5 to 10 years. Maybe we should be more aggressive in our research reports and describe what we in agriculture are working toward. We have a scientific capacity here that is compelling and we have too long been in the closet on so many of these important issues. Sometimes we are our own worst enemies; for the first 15 years of crop genetic engineering, many public plant breeders were saying that GM would not be a useful to agriculture. We have a lot to do in our own universities. At most university campuses on which I speak, there are students of agriculture, among others, who have reached the conclusion that GM crops and foods are not good for the environment and not good for health. They have either not been taught the facts, or the available information has not been taught correctly. If we can't get it right in our own schools of agriculture, how can we expect the mom with three kids to think that GM foods are okay? This is not something that I thought about just last night, but something that has been happening for a number of years. It will be interesting to see if Dennis Gonsalves⁹ feels the same way.

⁸Association of Public and Land-Grant Universities.

⁹Pages 37–46.

We have really failed in our schools of agriculture and colleges of arts. People at the little college I went to in Indiana thought that Vandana Shiva walks on water. When I gave a lecture there, some were sure that I was a devil from Monsanto. It's an amazing thing. Anti-science people, or at least those who are anti-modern agriculture, are from a small percentage of the population who demand policies based upon their voices. Perhaps we in the field did not do our jobs in the early years; so what should we do now, 20 years later? I'm not sure, and that's why I ask rhetorically, "Why can't you get it done?" I don't know if we have yet formulated a good suggestion of what to do to counter the mistruths that are being promulgated about GM foods.

Chris Dzuik (H-E-B, San Antonio): I work for a retailer and we try to be transparent with our customers. With the pink-slime issue, the social media took over and a product that was acceptable is now gone. With new technologies such as irradiation, we can refute what some of the activist groups are saying through research. How can I, as an employee of this company, contradict what we see on social media, such as posters saying that GM creates autistic children, allergens, and so on. Where would I go to find good data?

Beachy: I don't think it's at a single location or website; nor is the information being used in way that is reaching those who want useful information. Of the population who are against GM foods, I would venture to guess that many are also against childhood vaccines. An article by Marcel Kuntz in the October 2012 issue of *EMBO Reports*, asked the question, "In the postmodern assault on science: If all truths are equal, who cares what science has to say?" If religious truth or philosophical truth or the truth from a blog is equal to the truth of science, and policymakers consider them to be equivalent, then how do we expect to move forward? I suspect that many who are attending this meeting can agree that we have a science-literacy problem; we as scientists also have a believability problem, and for some there is a trust problem.

Bolormaa Jamiyansuren (University of Minnesota, Minneapolis): I do research on international trade of GMO products. How do you see the future for North American GMO producers, especially given that the competition is unfair. For example, the European Union had a strict labeling law that provided ample time for them to catch up with American producers, and now the law isn't so strictly enforced.

Beachy: I don't have a clear answer or a prediction about trade of GMO products. I happen to know a little bit about the China situation. A year or so ago, China said that they would not allow the growing of GM soybeans or corn, which some interpreted as a delaying tactic so that China could build its local industry before permitting cropping using foreign seeds. Meanwhile there has been a great deal of investment in agriculture and food-related science and biotechnology, and seed companies in China will soon market their own advanced seed varieties, and multinational seed companies may then be allowed to compete. With the use of non-tariff trade barriers such as this, I don't know if we can expect any legislative or judicial body to exact changes. And, Europe probably will go at its

own pace. I am more concerned about barriers that will be raised in Indonesia, Malaysia and Vietnam and other countries in southeast Asia. On the one hand, we have APEC¹⁰ and ASEAN¹¹ agreements that one would think could be unified around agriculture and food availability. If there were a willingness to talk across science and trade and if countries would agree to be part of a larger solution it would help the situation..

When I was in Washington, I was privileged to meet a few government officials, and I asked one of the ministers of agriculture in South America—I won't mention the country—"Would you be willing to work with our secretary to try to create an agreement amongst groups of producer countries with regard to trade of GM crops?" Remember, we have 26 or 28 countries that are producing and selling GM products; perhaps we could bring that group together to establish common goals and common cause. The minister said that if we could get a major country to lead it, *i.e.* the United States, they would join in. I didn't get the same reception when I mentioned it to our Secretary of Agriculture, in large part because of broader agriculture trade issues. There seems to often be a trade issue that interferes with cooperation in research and crop technologies. I'm being generalistic in some of these statements so please take them with a grain of salt, but many issues around trade do, indeed, prevent biotech cooperation, issues that are not-related to GMOs. We know what the challenges are, but we don't know how to get around them because we are often competing rather than cooperating with each other.

¹⁰Asian-Pacific Economic Cooperation.

¹¹Association of Southeast Asian Nations.

PART III–PLENARY SESSIONS

Session 1: Genetic Engineering and Specialty-Crop Improvement

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Transgenic Papaya Story: Still a Public-Sector Anomaly?

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I spoke at NABC 15¹, when the title of my talk was *The Papaya Story: A Special Case or a Generic Approach?* In the mid-1980s when we developed the transgenic approach, Roger Beachy and I were at the epitome of intellectual excitement. We believed that, in 10 years, the major crops would be improved through genetic engineering. The technology that led to the development of virus-resistant papaya is beautiful, and yet when I end my talks these days, I ask, “Really, what has happened over the past 25 years?” If we don’t address that question seriously, I’ll guarantee you that in 10 years or even 25 years from now we will be asking, “What happened?” At the end of my talk, we’ll see whether my transgenic papaya story is a public-sector anomaly, or whether that approach is widespread.

Figure 1 shows a beautiful, delicious Hawaiian papaya. Roger Beachy and I became virologists because we wanted to fight virus diseases. Figure 2 shows the symptoms of



Figure 1. Virus-free papaya in Hawaii.

¹*Biotechnology: Science and Society at a Crossroad.*



Figure 2. Papaya infected with ring-spot virus.

papaya ring-spot virus (PRSV), which has been in Hawaii since 1945. No natural resistance exists, and it is spread rapidly by insects.

ADVANCE OF PRSV

In 1978, the dean of the College of Agriculture pointed out to me that the virus—having destroyed the papaya industry in Oahu—had been identified in Hilo, just 19 miles from Puna where 95% of Hawaii’s papaya’s was grown (Figure 3).

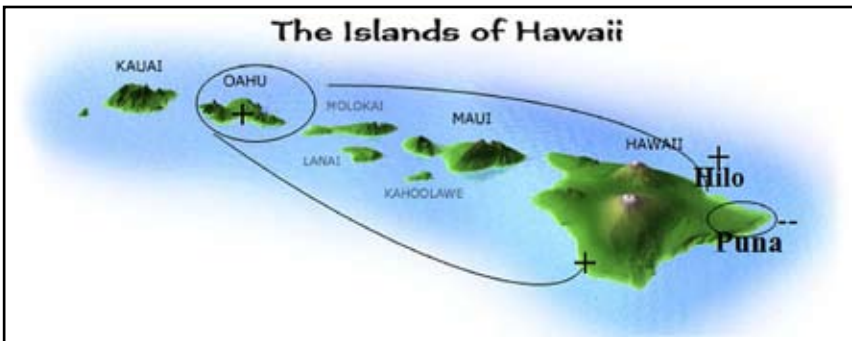


Figure 3. The potential problem.

He suggested that I do some research to try to develop a means of control. So, way back then, in 1978, we started by working up a rapid detection method, and then developed the pathogen-derived resistance method that Roger Beachy talked about². Basically, by the mid-1980s the concept (Figure 4) had been proven with virus-resistant tomato.

²Pages 19–28.

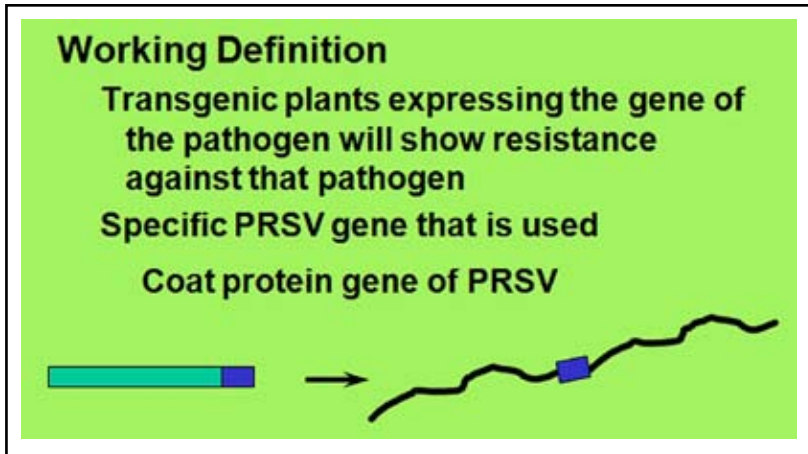


Figure 4. Pathogen-derived resistance.

We decided to take the coat-protein gene of the virus and place it in the chromosome of the papaya, in the hope that it would induce resistance, although, back then, in 1984 when we started, DNA sequencing was difficult as was cloning. And the dogma at that time was that resistance was coat-protein mediated, whereas our papaya ringspot had no natural start signal. So we actually added some amino acids from the cucumber mosaic virus to achieve a start signal.

I was fortunate in being at Cornell's Geneva Experiment Station, where John Sanford and his colleague had invented the gene gun. With Jerry Slightom, an excellent molecular biologist, and graduate student Maureen Fitch, we cloned the coat-protein gene in 1984, and Figure 5 shows the "father" of the gene gun in 1988. We were still using .22-caliber blanks to shoot in genes.



Figure 5. 1988–89, Maureen Fitch using the gene gun to transform papaya.

FIRST VIRUS-RESISTANT PAPAYA

Figure 6 shows a picture—taken at Cornell University in April 1991—of transgenic papaya line 55-1, which was a non-transgenic ‘Sunset’ transformed with the coat-protein gene inoculated with virus; the plant on the left contained the viral coat protein. This is where our group philosophy differed from the conventional wisdom of finding out if progeny indicated single-gene resistance. Instead, we cloned plants from tissue-culture, put them in the field and, within a year, our first trial was in progress.



Figure 6. 1991: Virus-infected papaya, genetically engineered plant on left.

By April 1992, cloned plants of this line were in the field in Oahu to see if resistance occurred. The long-awaited presence of the virus in Puna was reported in May 1992. Figure 7 shows devastation that occurred in 1994.



Figure 7. Puna: 1994.

Having proven the concept, Richard Mashardt backcrossed the female line 55-1 with the non-transgenic sibling Sunset until line 55-1 was homozygous for the coat-protein gene; he called this cultivar ‘SunUp.’ Growers wanted yellow flesh, so he made an F1 hybrid of ‘SunUp’ and non-transgenic ‘Kapoho’ to come up with transgenic ‘Rainbow’



Figure 8. Transgenic ‘Rainbow’ surrounded by non-transgenic papaya.

papaya. He utilized the field of less than an acre at the Waimanalo Experiment Station on Oahu to develop all this within three years of our first field test in May 1992.

Figure 8 shows a solid block of transgenic ‘Rainbow’ surrounded by a non-transgenic line in a field trial in Kapoho. There was no question that the transgenic approach was working, and growers saw it and requested it. We told them that they could not have it until after deregulation. But who would finance the deregulation of a public-sector project? John Sanford and I applied for an NSF grant, without success. The team’s first grant for the papaya work was for about \$25,000.00 for three years—special funds through Senator Inouye—it was no million dollars.

RED ZONE AND RELEASE

So, we scientists entered the “red zone” (Figure 9). I had never done any regulatory work, but it was necessary if we were to help the growers. Back then it was easier than it is today; the process is represented in Figure 10. I recall a meeting when growers suggested that the technology would be too expensive for their adoption because Monsanto would likely charge \$10 million. They had read that in the newspaper. Within a year, the Papaya Administrative Committee (PAC) had the license, and Monsanto did not charge a dime for it, showing that it’s a mistake to rationalize yourself out of doing something.

In May of 1998, almost 6 years to the day after the virus was discovered in Puna, we were able to release seed to growers. If we had started our research after the virus had reached Puna there would be no papaya industry in Hawaii today. I’m not a philosopher, but I would say that if, under the best circumstances, something is likely to take time, start on it immediately. If timing is critical, don’t wait until you have the ultimate answer. Use best judgment and move forward (Figure 11).

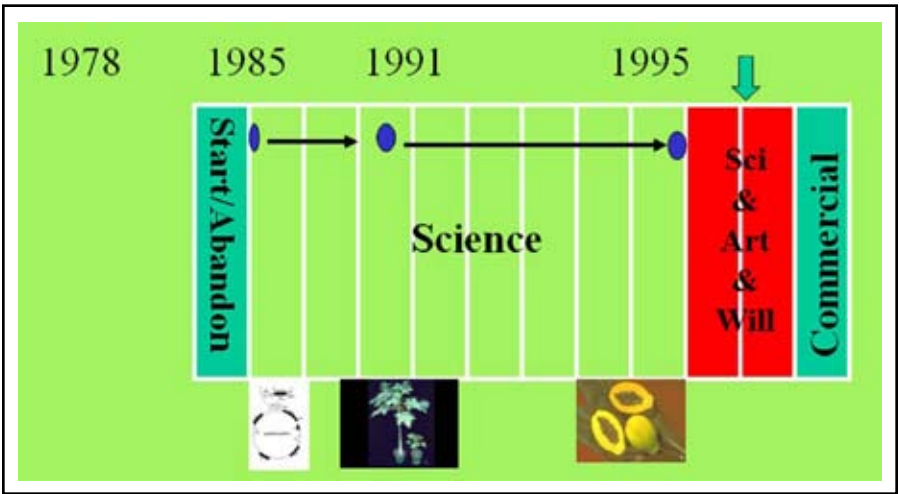


Figure 9. Hawaiian transgenic papaya (1995):
Entering the red zone of translational biotechnology.

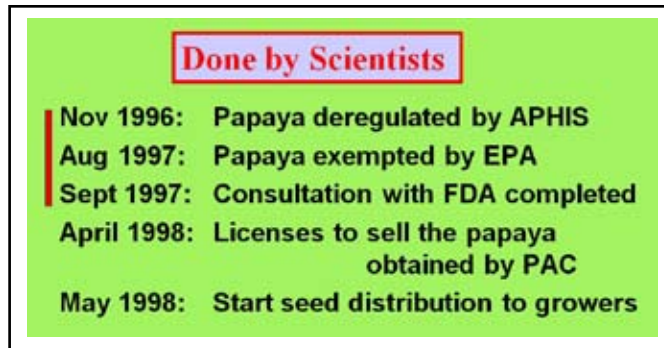


Figure 10. Deregulation and commercialization.

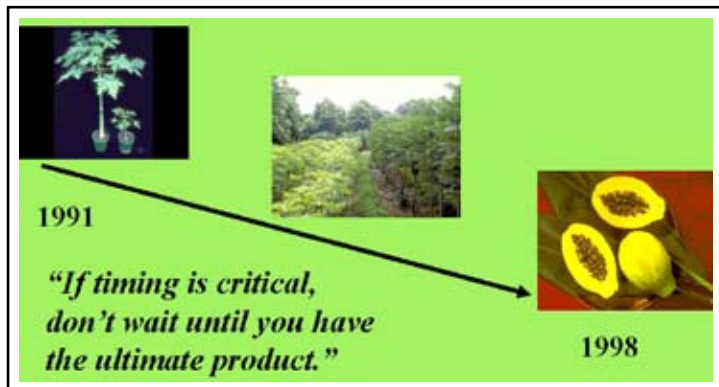


Figure 11. Under the best circumstances, it takes time.

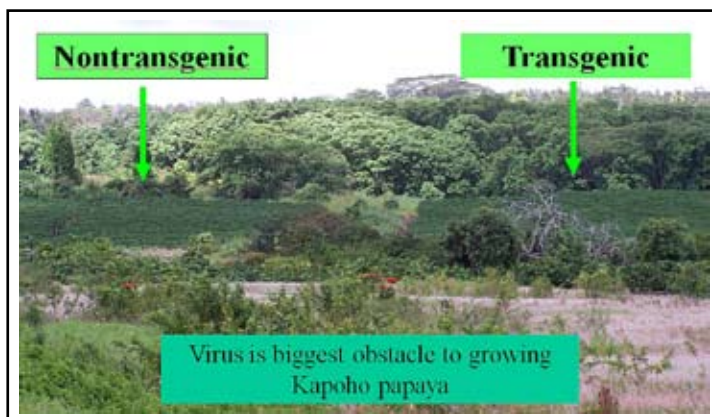


Figure 12. Coexistence under an identity-preservation protocol.

DEREGULATION ELSEWHERE

In Hawaii, we've been growing non-transgenic and transgenic papaya for more than a decade, because Japan, until recently, imported only non-transgenic papaya. This was achieved using identity-preservation protocols. Figure 12 shows a photograph taken in 2004, an example of the few fields where this applies. The most pressing problem isn't gene flow, it's loss of the non-transgenic crop due to the virus.

Deregulation in Canada was rapid because they acted on information from the United States. We started trying to deregulate the papaya in Japan a year after it was commercialized in the United States in 1998; it's a long story, but in December 2011 it was deregulated.

There is a common misperception that the Japanese consumer would be reluctant to buy it because it was labeled as being genetically modified. We went there expecting that with the first shipment of papaya, which was sold at Costco Japan. The most prevalent questions were, "How expensive is it?" and "Does it taste okay?" The Flavr Savr™ tomato failed not because it was genetically modified, but because it was unpopular. If you have a good product, consumers will buy it.

ADDRESSING THE CONTINUING THREAT

In 2001, I said, "Don't forget the past," and Figure 13 contrasts the papaya situation then with how it had been in 1994. This is particularly appropriate now because a bill was recently introduced by a councilwoman on the big island in the county of Hawaii to ban all GMOs on the island of Hawaii where nearly all of the papaya is grown. The GM papaya would be "grandfathered" in, but would be grown under BSL-3 conditions. That bill was voted down. On July 2nd they changed the wording to require a 750-ft buffer zone

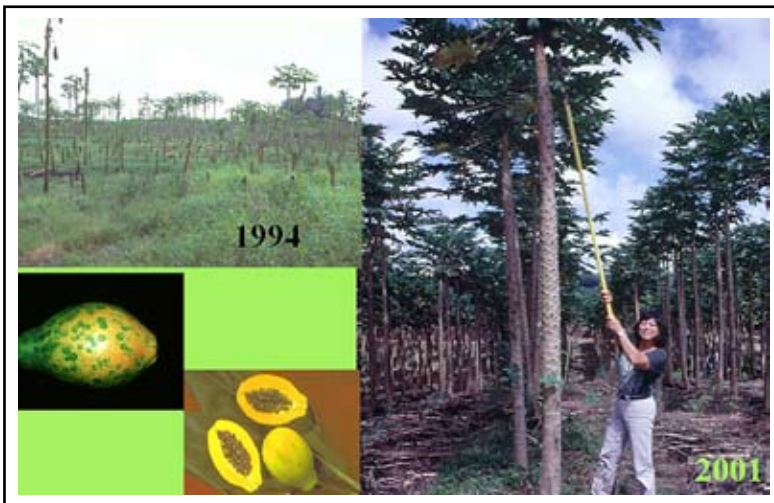


Figure 13. Don't forget the past.

between transgenic and non-transgenic papaya, which farmers are unhappy about. Now that I'm retired and a private citizen, I say that enough is enough. Papaya is the cheapest, most nutritious fruit in Hawaii. Four may be purchased for only a dollar in a farmers' market in Hawaii. This is the message that consumers must get across to the politicians. Some 85% of papaya now grown in Hawaii is transgenic. It's reasonably priced, and it tastes good; it's better than non-transgenic papaya. Figure 14 shows why farmers avoid non-GM genotypes: PRSV is still a serious threat.

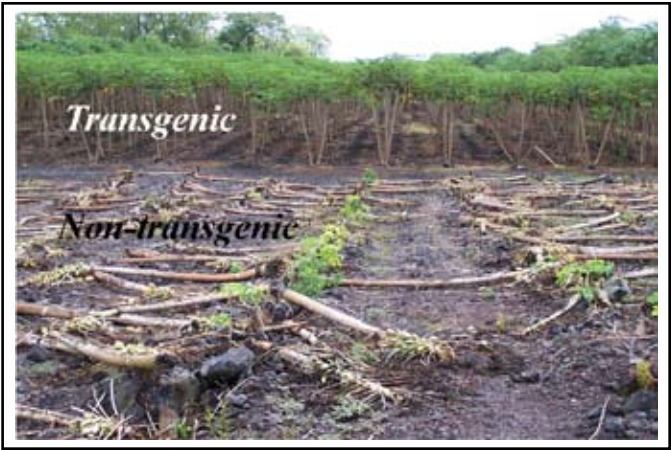


Figure 14. 2011—transgenic papaya at 85% of production. PRSV remains a threat.



Figure 15. 1997—transgenic papaya brought to Thailand.

THAI STORY: THE HUMAN ELEMENT

In 1994 we were asked to help tackle PRSV in Thailand. In our lab, Thai scientists developed locally adapted transgenic genotypes, which, in 1997, we hand-carried to Thailand. They worked beautifully in field trials. However, due to politics and lobbying of activists, our transgenic papaya will never be available to the Thai consumer and serious damage from the virus will continue to affect production and compromise the living standards of those who are most vulnerable (Figure 16).

In 2013, is transgenic papaya still a public-sector anomaly? Absolutely. We must continue our efforts in the red zone, dealing with people and with politics. We must bring the human element into the picture. What will the next 25 years bring? I hope it will not be the same old story.



Figure 16. Keep the human element in transgenic efforts.



DENNIS GONSALVES was born and raised on a sugar plantation in Hawaii. He was the director of the USDA Pacific Basin Agricultural Research Center in Hilo, Hawaii, from 2002 until his retirement at the end of 2012. He received his BS in horticulture (1965) and MS in plant pathology (1968) from the University of Hawaii, and his PhD in plant pathology (1972) from the University of California at Davis. He worked at the University of Florida from 1972 to 1977 and at Cornell University from 1977 to 2002, rising to the endowed position of Liberty Hyde Bailey professor in 1995.

Dr. Gonsalves does fundamental and applied research to control plant viruses. He was appointed to the Agriculture Research Service Science Hall of Fame in 2007 and received the Presidential Distinguished Rank Award in 2009. He led the team that developed—through the public sector—the virus-resistant transgenic papaya that saved the papaya industry in Hawaii. For this work, they received the Alexander Von Humbolt Award in 2002 for the most significant accomplishment in American agriculture in the previous five years.

Benefits of Biotech Specialty Crops: The Need for a New Path Forward

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As an entomologist, I work on insects affecting vegetables. This puts me in an interesting situation because every year when I see the ISAAA¹ reports—showing rapid growth in cultivation of genetically engineered soybean, maize, cotton and canola—I say, “Where are the vegetables? Where are the specialty crops?” It’s ironic that the second crop to be transformed, by Monsanto, was tomato, for resistance to tomato fruitworm (*Helicoverpa zea*²), with a *Bt* protein. That was in 1985 or 1986, and yet we don’t have any tomatoes on the market that are genetically engineered to resist insects. I keep hoping that the next ISAAA report will contain data on vegetables.

Vegetables are an important part of the human diet. Calories can be provided by cereal crops, but for nutrition—especially in the developing world, where malnutrition, or “hidden hunger,” is prevalent—promotion of vegetables is needed. I’m not a vegetarian, but I eat a lot of vegetables; they’re good for you, we need more of them in the human diet.

INSECTICIDES APPLIED TO VEGETABLES

Vegetable farmers usually earn higher incomes per unit area compared to cereal producers. Vegetables are high-value commodities, but high cosmetic standards are applicable, as for papaya (described by Dennis Gonsalves³). Many are eaten fresh, which means that they’re intensely managed with frequent use of “traditional” insecticides. The data in Figure 1 will surprise a lot of people. It shows that worldwide insecticide use on major crop groups costs \$10.6 billion. Some 45% of the value of insecticides used is applied to fruits and vegetables. Furthermore, the amount applied to fruit and vegetables is 1.5 times higher than the total applied to cotton, corn and rice. So, the fresh products that we want to encourage people to use are getting blasted by insects and diseases.

¹International Service for the Acquisition of Agri-Biotech Applications.

²Also known as the cotton bollworm and corn earworm.

³Pages 37–46.

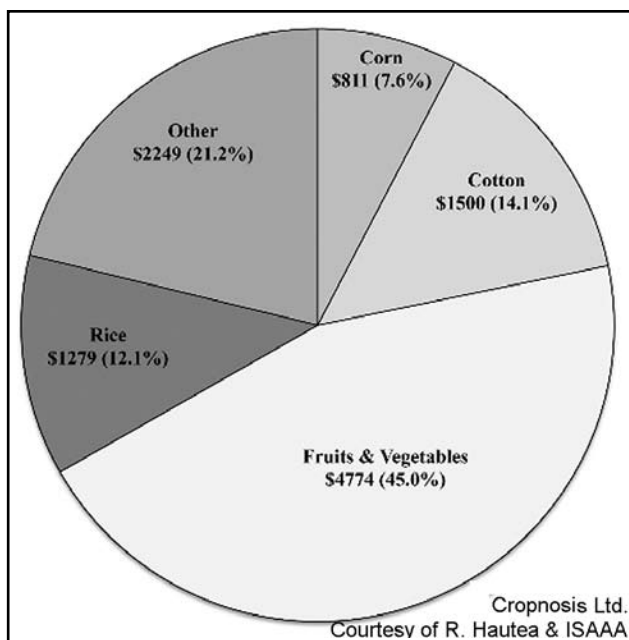


Figure 1. 2010 worldwide insecticide use on major crops (millions of US\$).

After receiving an undergraduate degree in philosophy, I wanted to do something practical. Being interested in environmental issues, food security issues, and biology, like a lot of colleagues my age I read *Silent Spring*. In the last chapter, “The Road Forward,” Rachel Carson says, “Why don’t we use things like insect viruses, insect bacteria, insect fungi, and pheromones to control insects? Why are we using DDT and organophosphates and carbamates?” That resonated with me. So with my little philosophy degree in hand, I went to graduate school in entomology. I’ve always remembered *Bacillus thuringiensis*, a most interesting bacterium. Many strains exist, very safe for humans and the environment. I used it as a foliar insecticide in my graduate research. You’d spray it on and you’d have to spray it on two or three days later because it broke down so quickly in sunlight. Then someone had an idea: Why don’t we engineer into plants the gene for producing the insecticidal protein? And now this second- or third-rate foliar protein is present on about 70 million hectares worldwide, in maize, soybean and cotton.

Bt POTATO

We haven’t had a great track record with *Bt* vegetables. The first was *Bt* potato, commercialized in 1995 to control the Colorado potato beetle, a primary defoliator in North America and Europe, resistant to many insecticides, with control costs of \$140 to \$300 per acre. When *Bt* potato appeared—a Monsanto product—growers liked it. In the second year it doubled in sales, and in the third year it doubled again (Figure 2).

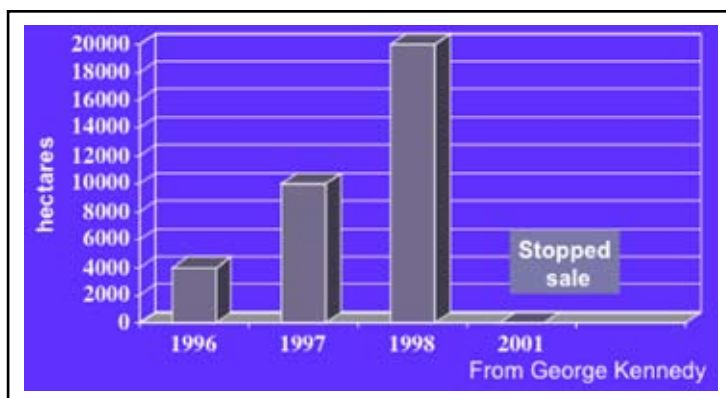


Figure 2. Rise and fall of *Bt* potato.

However, by 2001, it had fallen by the wayside. There were biological reasons, business-management reasons, and social reasons for the demise of the *Bt* potato:

- It controlled only Colorado potato beetle. It didn't affect aphids or leafhoppers.
- Only one *Bt* variety was available. Granted it was Russet Burbank, which is commonly grown.
- There were sporadic yield problems.
- The need for refuges—planting a non-*Bt* variety nearby—was new to potato growers.
- There was debate on the safety of GMOs, and
- Market consolidation.

Most ironically, a new class of insecticides, the neonicotinoids, had become available in 1995. They controlled aphids and leafhoppers as well as Colorado potato beetle. One new science technology won over another. It's noteworthy that neonicotinoid insecticides are now making the front pages of newspapers because of concern over killing bees and other organisms—and we still don't have *Bt* potatoes.

Bt EGGPLANT

At Cornell, we are trying to bring new technologies to developing countries. The eggplant fruit and shoot borer (Figure 3) is a caterpillar that farmers “traditionally” try to control by spraying a cocktail of organophosphates, carbamates and pyrethroids, each of which has some human toxicity (Figure 4). This approach doesn't work too well. Sometimes 80 sprays are required on a crop that reaches maturity in 80 to 90 days.

Mahyco, a seed company in India, produced *Bt* eggplant. Figure 5 shows Dr. Usha Barwale Zehr from Mahyco giving seed of genetically engineered eggplant to Dr. C. Ramasamy, vice chancellor of Tamil Nadu Agricultural University, who will pass it along to his plant breeders for incorporation of the *Bt* trait into locally grown, open-pollinated varieties. The idea is for Mahyco to sell these as hybrids to make some money, but also to disseminate the technology. The superior performance of *Bt* eggplant over its non-genetically engineered, repeatedly sprayed, counterpart is clear in Figure 6.



Figure 3. Eggplant infested with fruit borer.



Figure 4. “Traditional” control of eggplant fruit and shoot borer in India. Although insecticides are toxic, farmhands are often unprotected.



Figure 5. A gift of *Bt*-eggplant seeds to the vice chancellor of Tamil Nadu Agricultural University.



Figure 6. *Bt* eggplant (right) compared with its non-GM counterpart.

The *Bt* eggplant (locally “brinjal”) went through ten years of field trials, and safety trials, and then Greenpeace entered the piece. Figure 7 shows a protest in Tamil Nadu. The woman, an activist, is giving a member of the state legislative assembly what she called the “last non-GM eggplant” that will be had in Tamil Nadu if the *Bt* genotype is commercialized. Greenpeace is good at attracting publicity, whereas we try to talk science to



Figure 7. Activists present a GM-free bouquet, including eggplant, to a state assembly member to protest GM-food-crop commercialization and research in Tamil Nadu.

people and it doesn't always work. Greenpeace also held monthly anti-GM seminars by scientists, including Gilles-Eric S  ralini (University of Caen, France) and Jeffrey Smith (Institute for Responsible Technology, Iowa) and disrupted a field trial at Tamil Nadu Agricultural University

It has been estimated that Greenpeace spent \$100 million to derail *Bt* eggplant. Under what pretense? They have admitted that they see GM as a good fundraiser, something that garners public attention. Greenpeace can talk about global warming, over which people feel they have little control. In contrast, they do feel control over the products they consume. Consequently, Greenpeace has focused on GM, to their detriment as a credible NGO.

What's the final story? The minister for the environment, the last gatekeeper for *Bt* eggplant in India, enacted a moratorium in 2011, which is where it now sits. One lesson is that you can't outspend Greenpeace; they have deep pockets. If there is no political will, registration will not occur. On the other hand, if farmers have the will, things can happen. And if *Bt* eggplant is deregulated and commercialized in Bangladesh right next door, it will probably make its way into India, as did *Bt* cotton, which came into India before it was legal, smuggled in from somewhere. You can't control this technology if growers really want it. Of course, it would be much better if the minister for the environment had the political will to deregulate the genetically engineered, insect-resistant genotype.

Bt SWEET CORN

Bt sweet corn in the United States is a more successful story. It's a *Bt*11 event from Syngenta that was registered for field corn and then crossed into sweet corn. Commercialized in the mid-1990s, the ride since then has been interesting (Figure 8). In 1999 it was grown on about 30,000 acres in the United States, and then, at about the same time as the controversy over the *Bt* potato, it crashed. However, since 2000, the acreage has steadily increased showing that growers like it. Despite export concerns for processors, farmer-adoption continues and in 2008 (the most recent data) it had ~9% of the total fresh market acreage.

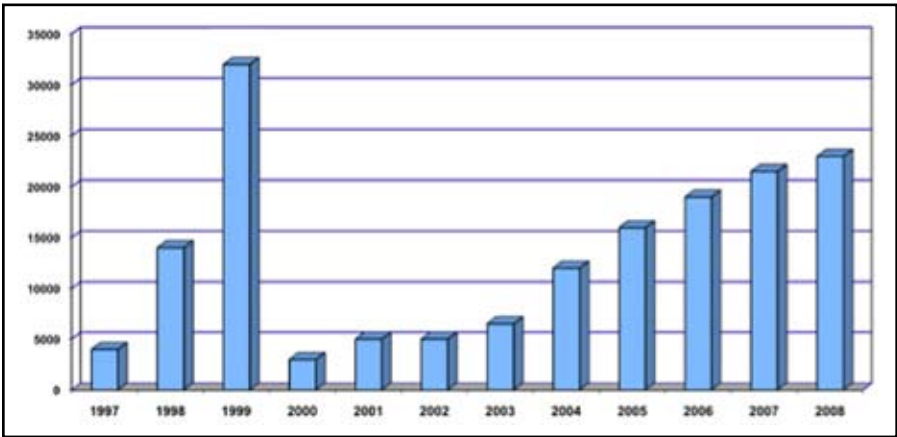


Figure 8. *Bt* sweet-corn product adoption in the United States (acres).

In 2011, Seminis Seeds came out with a two-*Bt*-gene version of their ‘Obsession’ sweet corn, which we field-tested in comparison with its non-*Bt* counterpart. We compared yields based on spraying either zero, four, or eight times with the insecticide “Warrior” (Figure 9). Without *Bt* and insecticide, only 6% of ears were marketable, with 94% unmarketable;

Clean ears (%) vs frequency of Warrior II application			
Variety	Applications of Warrior II		
	0	4	8
Obsession Plus (Bt)	100.0 ± 0.0a	99.0 ± 1.0a	100.0 ± 0.0a
Obsession	6.0 ± 3.5b	10.0 ± 2.0b	18.0 ± 10.9b
Means (±S.E.) followed by the same lower-case letters within a column are not significantly different (Fishers LSD means separation test, <i>P</i> >0.05)			

Figure 9. Evaluation of *Bt* sweet-corn varieties combined with Warrior II applications against Lepidoptera, 2010.

it was a bad year for corn earworm. Even when we sprayed eight times, only 18% of ears were marketable. ‘Obsession’ with two *Bt* proteins produced 99% to 100% marketable ears, even without insecticide. That growers like the technology is understandable.

In 2012, when this was coming to market, Whole Foods stated that they would not carry it, possibly because it was associated with Monsanto, which owns Seminis Seeds. Protestors sent 460,000 “anti” signatures via email to Walmart, the biggest food market in the world. To their credit, Walmart responded, “No. We are going to sell it. We looked at the science and we looked at our customers, too, and we said, ‘Yes. We will do it.’” Different customers go to Whole Foods from those who shop at Walmart, but more go to Wal-Mart rather than to Whole Foods.

VIRUS-RESISTANT BEAN

In Brazil, Embrapa¹ scientists are producing a virus-resistant common bean (*Phaseolus vulgaris*). They have worked for 10 years to achieve resistance to bean golden mosaic virus, which is transmitted by a white fly (*Bemisia tabaci*). It has been estimated that annual losses from BGMV would feed 18 million Brazilians. They expect it to be commercialized in 2014 or 2015, since the Brazilian government has the political will and they have scientists like Dennis Gonsalves² with the passion to carry things through.

EVENT-BASED REGULATIONS

Will there be other products to come? I keep asking myself why genetically engineered, specialty crops are not more widely used. Roger Beachy³ touched on many of the reasons. Event-based regulations—as an entomologist, this really floors me. What is the rationale for putting together a regulatory package on a Cry1Ab protein for tomato, when we know so much about it in other crops? Why do we need a new set of studies on non-target organisms? Or on allergenicity? The process should be streamlined to put this technology out where it’s really, needed. The *Bt* sweet corn actually piggybacked on field corn. Groups of crops may be packaged together, such as tomato, crucifers and other vegetables that are relatively small markets in which large companies have little interest.

PUBLIC-ACCEPTANCE CRITERIA

I’m also interested in public acceptance of GM products. Gonsalves pointed out that the genetically engineered papaya looked good and tasted good, which is why it has achieved broad consumer acceptance. A couple of studies suggest that consumers in North America will accept *Bt* sweet corn. One of my favorite studies was in Canada at a farm market. A farmer labeled *Bt* sweet corn and conventional sweet corn. He labeled one as a GM product and explained that it expressed a bacterial protein that would kill insects but not harm people. The other product was labeled as having been sprayed with various traditional insecticides. The GM sweet corn outsold the conventional corn 60:40. Once people became informed, they choose GM.

¹Equivalent to USDA-ARS.

²Pages 37–46.

³Pages 19–28.

In a study in a Philadelphia supermarket, people looked at the quality of the sweet corn, the freshness, and if it was labeled “genetically engineered”; they really didn’t care. Quality was more important than how it was produced.

What about public-sector production of these vegetables? Figure 10 shows a list of genetically engineered specialty food crops—produced at land-grant universities in Colorado, Illinois, Michigan, New York, Missouri and North Carolina—and where they are in the regulatory process. In most cases, the target is a horticultural characteristic. In one case, in Illinois, the target is an anticancer compound. Transgenic specialty crops can dramatically reduce the need of traditional pesticides. Dennis Gonsalves has shown this. Sweet corn evidence shows it also. But other characteristics would have even greater immediate appeal for consumers: products that will make them look better or change their health in some positive way.

Clearly, public education is essential, but it’s challenging. Surveys show that 50% of people do not want genes in their food, which reveals the scope of the problem. Perhaps broad acceptance will occur first in developing countries where food security issues are

Crop	Target	LGU	Process	Reg. Status	Constraint
Apple	Scab	CU	Intragenic	Not applied	Partner
Apple	Fire blight	CU	Gene express.	Not applied	Partner
Apple	Ornamental	CU	Knockout	Not applied	Partner
Apple	Flowering	IL	Transgenic	Not applied	Partner
Blueberry	Cold Tolerance	MSU	Transgenic	Not applied	Consumer
Blueberry	Herbicide Tol.	MSU	Transgenic	Not applied	Regulation
Blueberry	Early Flowering	MSU	Transgenic	Not applied	Regulation
Blueberry	Cold Tolerance	MSU	Transgenic	Not applied	Consumer
Blueberry	Early Flowering	MSU	Transgenic	Not applied	Consumer
Brassica	Salt tolerance	MSU	Transgenic	Not applied	Partner
Brassica	Anti-cancer	IL	Transgenic	Not applied	Consumer
Celery	Herbicide Tol.	MSU	Transgenic	Not applied	Regulation
Cherry	Virus resistance	MSU	Transgenic	Not applied	Consumer
Citrus	Disease/Insect	TAMU	Transgenic	Applied	Regulation
Citrus	Insect res.	CU	Transgenic	Not applied	Partner
Grape	Fruit rot	CU	Transgenic	Not applied	Consumer
Grape	Bacterial res	CU	Transgenic	Not applied	Consumer
Grape	Disease res.	MO	Knockout	Not applied	Consumer
Peanut	Virus res.	MSU	Transgenic	Not applied	
Potato	Drought tol.	MSU	Transgenic	Not applied	Consumer
Potato	Late blight	MSU	Intragenic		
Potato	Disease/Insect	TAMU	Transgenic	Not applied	Regulation
Tomato	Nematode res.	NCSU	Amplification	Applied	Partner
Tomato	Virus res.	NDSU	Transgenic	Not applied	Licensing
Tomato	Disease res.	NCSU	Transgenic	Not applied	Licensing
Tomato	Vaccine	IL	Transgenic	Not applied	Partner

Figure 10. Genetically engineered specialty food crops: research, regulation and constraints.

most acute. Technology may be developed in the United State, go out to developing countries, and then come back. But what really is needed is a political will. Political will and scientific evidence can be combined in an informed society to create good public policy. And that public policy can welcome products developed with modern science and biotechnology. It was very disappointing in India when the minister of the environment overrode his scientific committee. We need political will, we need scientific evidence, and we need social infrastructure with which to create policies that will foster the adoption of genetically engineered specialty crops (Figure 11) that benefit society.

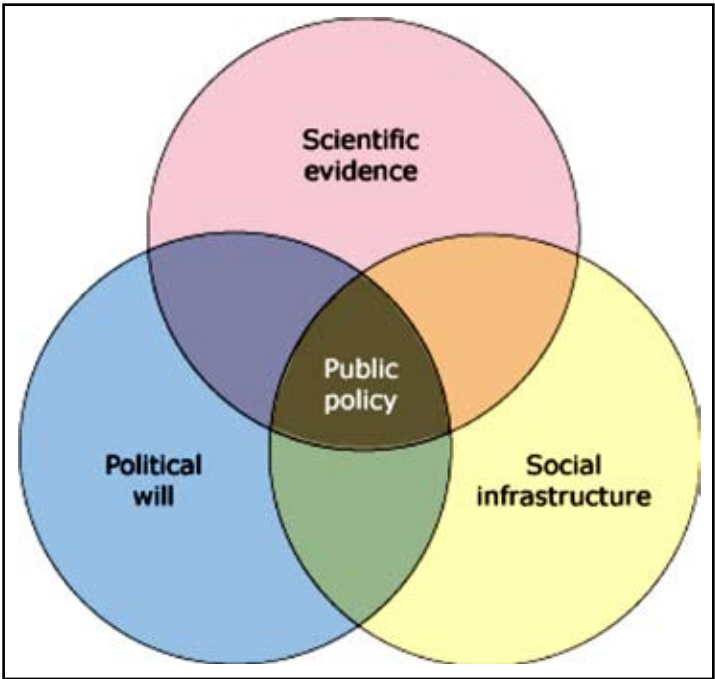


Figure 11. Factors necessary for the adoption of genetically engineered specialty crops.



TONY SHELTON is a professor of entomology and an international professor and associate director of international programs for Cornell's College of Agriculture and Life Sciences. He received his BA in classics and philosophy from St. Mary's College of California, and worked in business before returning to graduate studies at the University of California, Riverside, where he received his MS and PhD degrees. He began his academic career at Cornell in 1979 where his research focuses on developing sound insect-pest-management strategies for vegetables with spin-offs for other crops. Components of his program include insect population ecology, biological control, plant resistance, agricultural biotechnology, insecticide resistance, and risk assessment of insect-resistant genetically engineered crops. His program has a strong commitment to outreach education for the agricultural community, the general public and international agriculture, especially in India and China.

Dr. Shelton served as the associate director of research at the Cornell Experiment Station from 1993 through 2001. Among the awards he has received are the Entomological Society of America's Award for Integrated Pest Management and its Recognition Award for Research. He is a fellow of the Entomological Society of America.

Potential Concerns of Different Stakeholders to Genetically Engineered Specialty Crops

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This presentation has two separate sections. The first attempts to summarize and explain some potential concerns that different non-governmental stakeholders might have with genetically engineered (GE) specialty crops. It is based upon a review of publicly available written documents from those organizations and review of their internet websites, and does not reflect my views or the views of Center for Science in the Public Interest. The second section of the presentation is the Center for Science in the Public Interest's view on some issues that GE specialty crop developers should consider as they develop those crops and bring them to market.

PRODUCT-SPECIFIC CONCERNS

When preparing this presentation, I looked for product-specific concerns—related to GE specialty crops—that have been voiced by different organizations. Surprisingly, I found few concerns related specifically to specialty crops. I looked through the dockets on the GE plum and the GE apple¹ at USDA and searched websites of stakeholder groups and found that most of the concerns raised are not related to specific applications.

I did find some specific concerns over a virus-resistant plum, which has been approved but is not yet commercialized. The Organic Consumer Organization had doubts over the stability of the inserted genes and raised concerns over potential effects on bees and other pollinators. With other organizations, they pointed out the absence of short- and long-term safety testing and feeding trials for toxicity and other effects. The Sierra Club also was fairly vocal at that time, and they raised some issues around potential harm to local bee communities. They suggested the potential for creation of new viral forms via

¹Pages 87–94.

recombination, and even doubted the safety of eating viral proteins. Many would take issue with the validity of these concerns; I mention them to illustrate the kinds of product-specific questions that have been raised.

The initial public-comment period that is part of the on-going review of the GE apple elicited the following concerns from the Center for Food Safety in Washington, DC:

- Changes in resistance to pests and pathogens may occur as a result of the suppression of polyphenol oxidases.
- Cut and packaged apple slices may support the growth of pathogenic microorganisms.
- The nutritional status of the cut apple slices may be unpredictably affected by storage and packaging conditions.

GENERAL CONCERNS

I was surprised to discover that many of the objections to specialty crops are not product-specific. Instead, they are what I call generic concerns—objections to GE crops in general rather than to any specialty crop in particular. Similar objections could be leveled at corn, soybean, apple, plum, broccoli or whatever. I won't attempt an exhaustive coverage; I did look at the website of the Center for Food Safety to examine their concerns regarding food safety for GE crops in general. They posed the question, "What are the new 'unexpected effects' and health risks posed by generic engineering?" and answered it by listing six areas:

- Toxicity
- Allergic reactions
- Antibiotic resistance
- Immuno-suppression
- Cancer
- Loss of nutrition

They explained why they thought that each of these could be linked to genetic engineering. They had similar information for the environmental area, but this provides a good example of what consumers are hearing from this group regarding the safety of GE ingredients in food.

Food and Water Watch, an environmental group, issued a report in 2011, *Genetically Engineered Foods: An Overview*, providing their perspectives on GE foods. The following are quotes from the overview, illustrating their concerns over GE crops and the foods made from them:

Genetic contamination is a serious threat to the livelihoods of non-GE and organic farmers who bear the financial burden of these incidents.

The environmental effects of GE crops can include intensified agrochemical use and pollution, increased weed and insect resistance to herbicides and pesticides, and gene flow between GE and non-GE crops.

The Roundup Ready trait lowers the nutritional content of crops by inhibiting the absorption of nutrients, including calcium, iron, magnesium and zinc, making the plants more susceptible to disease.

The second statement reflects a commonly expressed concern that the environmental effects of GE crops include increased agrichemical use and pollution, increased resistance of weeds and insects to herbicides and pesticides, and the likelihood of gene flow between GE and non-GE crops. I had never come across the third statement before. Many other concerns are provided in that report; these three provide just a “flavor.”

OPENING THE FLOODGATES

Now I come to even more general concerns. One that appears frequently in literature from consumer and environmental NGOs is the idea of “precedent,” that approval of a particular GE crop will somehow “open the floodgates.” A quote from one of these is:

This is simply a Trojan horse to get more GE foods and crops on the market.

The Organic Consumer Association expressed it thus:

The approval of GE plums would be a precedent-setting step by the USDA opening the floodgate for more GE trees including fruit, nut, ornamental and paper-pulp species as well as trees engineered for soil remediation and other traits.

Similarly, people expressed opposition to GE alfalfa during the deregulation process, on the grounds that it would set a precedent. So that’s an argument that one needs to be aware of in this field.

CONTAMINATION

From the Sierra Club:

The organic and conventional plum markets in the United States will quickly be threatened by the first GE plum tree that will contaminate organic and conventional plum orchards once it is approved...

This espouses the notion that GE crops will “contaminate” organic and conventional crops.

A similar doomsday scenario has been suggested by Friends of the Earth and Food & Water Watch:

There could be significant economic impacts to conventional and organic orchards if their apples are contaminated with GE applies...

Concerns over co-existence and contamination are commonly raised with respect to GE corn, and somewhat less so with respect to GE soybean.

MANDATORY LABELING

The demand for mandatory labeling of foods containing GE ingredients is another general issue raised for all GE products, including specialty crops. It has become a vocal movement in numerous states, having started in 2012 with the California Ballot Initiative, which

didn't pass but garnered national press and publicity. Much of the discussion underpinning it revolves around the issue of "right to know": consumers have the right to know what's in their food. A second issue surrounding those calling for mandatory labeling is that they say consumers are not sure that GMO food is safe so it should be labeled so that they can choose not to eat it. A third argument is often seen: if it is safe and beneficial, why hide it? I raise this because it could become a greater issue for specialty crops—which are consumed directly—than for corn or soybean, considering that the latter crops enter the human food chain mainly as highly processed ingredients such as corn oil, soy lecithin, high-fructose corn syrup, *etc.*

The Genetically Engineered Foods Right-to-Know Act, introduced in April 2013 by Senator Barbara Boxer from California and Congressman Peter DiFazio from Oregon, is a bellwether for the labeling issue. It would require labeling on whole foods and processed foods including fish and seafood. According to Senator Boxer:

Americans have the right to know what is in the food they eat so they can make the best choices for their families. This legislation is supported by a broad coalition of consumer groups, businesses, farmers, fishermen and parents who all agree that consumers deserve more—not less—information about the food they buy.

This statement is true of lots of things, not just genetic engineering.

Figure 1 shows the status of state-level food-labeling bills in June, 2013. The states in blue have bills proposed. Those in red have some approved. In New York in June, 2013, a food-labeling bill was voted down in committee. In contrast, the governor of Connecticut has stated his intention to sign a GE food-labeling bill, which has gone through both houses. However, it won't come into play until a certain number of neighboring states have enacted similar legislation. The implication is that Connecticut would be economically disadvantaged if it were the only state in the region with GE-food labeling.

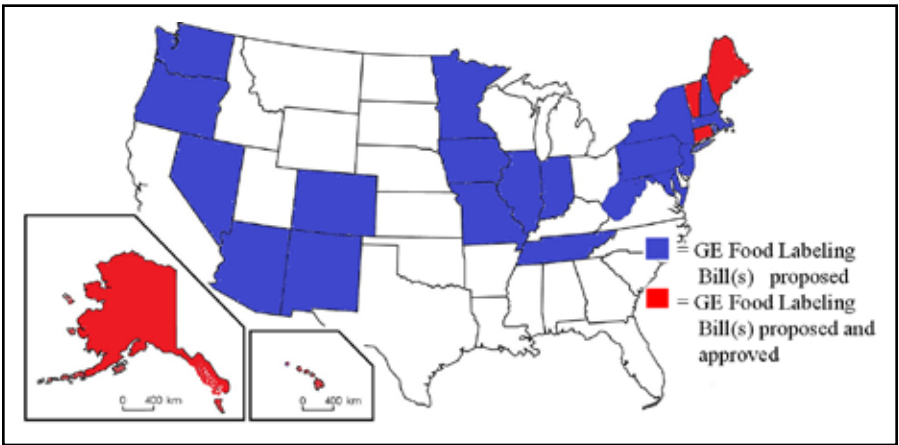


Figure 1. State-level GE food-labeling bills.

CSPI's VIEWS

The Center for Science in the Public Interest is a non-profit consumer organization located in Washington, DC working on food and nutrition issues. We advocate based on the best available science on behalf of consumers and try to educate consumers on the relationship between their health, their diet, and the food they eat. Our Biotechnology Project started in 2001, and we are devoted to reviewing the evidence and facts surrounding the GE crops grown in the United States. We have found that scientific evidence supports their safety, both to grow and to eat. The evidence also points to benefits accruing from growing some of those crops, either to farmers or to the environment, but not necessarily directly to consumers.

On the other hand, CSPI does believe that GE crops need to be assessed on a case-by-case basis, and we do push for functional biosafety regulatory systems that ensure safety while allowing safe products to be marketed. CSPI is supportive of streamlining regulations, where appropriate. The idea would be to have the regulatory system look carefully at crops and traits that are less familiar and potentially risky with more scrutiny, while facilitating deregulation of familiar and safe crops and traits in a streamlined fashion.

For those developers who wish to market GE specialty crops, CSPI believes there are two critical areas needed for overall product success with consumers in the marketplace. The first is ensuring there is comprehensive federal regulation and oversight that ensures consumers that the GE specialty crops are safe to eat and safe for the environment. Second, the developer must anticipate and address both consumer and customer acceptance issues, which involve market acceptance, coexistence, and transparency. These two critical issues will be discussed in detail below.

COMPREHENSIVE FEDERAL OVERSIGHT

By “comprehensive federal oversight” I mean:

- A statement from FDA that the GE crop variety in question is safe to eat,
- A full review by the USDA with necessary environmental analysis under the National Environmental Policy Act, and
- Appropriate risk assessment—what many in the industry might call “stewardship.”

FDA

The Food and Drug Administration regulates crops, including fruits and vegetables, under the Federal Food, Drug and Cosmetic Act, under which “food additives” go through a pre-market approval process, unless they are generally recognized as safe (“GRAS”). FDA determined that a GE crop is not a food additive and in 1992 set up a voluntary consultation process for GE plants to ensure that the GE plant was “substantially equivalent” to its conventional counterpart. To date, all those who have commercialized GE crops have complied with voluntary consultation. However, in view of the fact that food safety is a critical issue for consumers, we at CSPI are of the opinion that the voluntary consultation process is not sufficient. The reviews by FDA are not comprehensive. More importantly,

their stock response—“we have no questions at this time”—implies that Monsanto, or whoever is developing the product in question, remains responsible.

We believe that safety determinations by FDA are needed. When the GE-wheat issue hit in Oregon in May 2013, the most that could be offered by USDA in their press release was the wishy-washy comment that FDA had looked at it and had no questions at that time on its safety. Other countries have mandatory pre-market food-safety approval processes, and it's ironic that, in the United States, none of these crops can be planted without a mandatory review by USDA, yet we can eat the food from them without that. In 2004, Senator Durbin introduced the Genetically Engineered Foods Act—reasonable legislation in this area; it would take the voluntary process and mandate it without changing the safety standard or the data requirements. The FDA would formally approve the safety of each GE crop. It would not lengthen the process but it would give consumers confidence in the federal government's oversight. Support from those who are developing GE crops would help alleviate concerns both around labeling and the technology.

USDA

The United States Department of Agriculture needs to be involved in overseeing regulation of these crops to ensure against agricultural and environmental problems. The USDA's (non)position on herbicide-tolerant Kentucky blue grass—a GE variety developed by Scotts Corp.—is revealing. In 2010 Scotts requested a determination of the regulatory status of GE (glyphosate tolerant) blue grass; none of the DNA cassette (donor gene, promotor sequence, *etc.*) were plant pests and the gene gun was used to achieve transfection rather than *Agrobacterium*. Accordingly, the USDA responded in 2011 that this GE crop is not regulated.

I have been arguing for about ten years that the USDA regulatory system may not apply to some GE crops and now we actually have a decision by USDA that they will not regulate this crop. So, this GE Kentucky blue grass can be field-tested without any oversight, and it can go to market without any oversight. I raise this because some may be thinking, “Regulation is expensive. It takes time. We should do what Scotts did.” I would counsel against that for specialty crops. You need USDA oversight to garner consumer confidence and achieve market acceptance. At the same time, USDA needs to do a better job. There has been litigation over glyphosate-tolerant alfalfa and sugar beets, where courts have said that the USDA environmental analyses under the National Environmental Policy Act were lacking. In response to that, USDA now is in part doing an environmental impact statement (EIS) for the 2,4-D- and dicamba-tolerant crops. It is fundamentally important that USDA does its job well, that they assess environmental impacts, and that they avoid litigation. They don't need EISs in all cases or even in most cases, but they need to do a better job. They had gotten sloppy for a number of years, and the courts properly slapped them on the wrist. They have a new system in place that will, hopefully, be quicker and do a better job.

Finally, USDA needs to insist on appropriate stewardship. There's evidence of resistance to *Bt* in corn rootworms and of herbicide-tolerant weeds, possibly resulting from poor stewardship by farmers and some biotech companies. This technology has the potential

to be very beneficial for specialty crops. It should be used judiciously and as appropriate, depending on the biology of the specialty crop, with appropriate management practices to minimize the development of insect resistance to *Bt* and other insecticides, and to minimize the development of herbicide resistance in weeds.

ANTICIPATING CONSUMER ACCEPTANCE

The second issue is to anticipate and address consumer and customer acceptance, which involves:

- Market acceptance
- Coexistence
- Transparency—right to know

Market Acceptance

To achieve market acceptance of a product, there is need to educate, inform and listen to the farmers and relevant farm organizations. There is need to listen to food-chain actors and to educate them, including grocery stores, as well the media, regulators and politicians.

Coexistence

Coexistence is the concurrent cultivation of biotech, organic, and non-biotech varieties of the same crop. It depends on the biology of the crop and the production system. It is different for corn than for soybeans than for apples. It requires setting up appropriate processes in the food chain. I raise this issue because it may be increasingly important in the future, depending on the crop. We saw this in terms of concerns raised by environmental consumer groups at the beginning of this presentation, and I think it's important to put in place procedures to segregate seed. Any inadvertent commingling will have minimal effect as long as there's a segregated seed supply. To me, that is key.

Transparency

Finally, on the transparency issue, CSPI is not in favor of mandatory GE labeling. We do think that there should be consumer access to information about whether their product is genetically engineered, so for the consumer who wants to know, they should be able find it. It shouldn't be hidden, but that's different from having a mandatory government-imposed label. We do think that that information should be available whether it's on a website or electronically; there's a host of different ways to make information available these days. But, with that, there needs to be information about the benefits of these products, as well as information about the production process. Consumers don't know a lot about how their food is produced or where it comes from, so hearing "genetic engineering" out of the agricultural context can be confusing. There needs to be better education and transparency all around.

IN CONCLUSION

We need strong, but not stifling, regulation to reassure consumers. I call it "appropriate regulation." It can be streamlined by using preexisting data. There is no reason to reinvent the wheel, but the primary emphasis should be on issues that pose the greatest potential

risk and issues that are most unfamiliar. We want beneficial products and education to explain those benefits and their production process. I think that's really important. People don't know a lot about the quantities of pesticides used in producing unblemished fruits and vegetables. If they did understand that, there might be a different view about using technologies to reduce agriculture's environmental footprint. As I said, transparency is essential but not necessarily mandatory labeling. It is more important to be aware of general concerns related to GE crops. Genetically engineered specialty crops are not going to be treated differently by consumers who have concerns or objections to GE in general.

FURTHER READING

Jaffe G (2012) Straight Talk on Genetically Engineered Foods: Answers to Frequently Asked Questions. <http://cspinet.org/new/pdf/biotech-faq.pdf>.

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GREGORY JAFFE is director of the biotechnology project for the Center for Science in the Public Interest (CSPI), an advocacy and educational organization that focuses on nutrition and health, food safety, alcohol policy, and sound science. CSPI was instrumental in pushing through the federal law to create the Nutrition Facts label with clear nutrition information and that set standards for nutrition and health claims on food labels. CSPI is supported primarily by 800,000 subscribers to its Nutrition Action Healthletter.

Mr. Jaffe first worked as a trial attorney for the US Department of Justice's Environmental and Natural Resources Division for seven years. He then moved on to become senior counsel with the US Environmental Protection Agency Air Enforcement Division, before joining CSPI to direct the biotechnology project. He is a recognized expert on the US regulatory structure for agricultural biotechnology as well as consumer issues pertaining to agricultural biotechnology.

He earned his BA from Wesleyan University in biology and then received a degree from Harvard Law School.

Genetic Engineering and Specialty-Crop Improvement

Q&A

MODERATOR: DAN LINEBERGER

*Texas A&M University
College Station, Texas*

Tom Redick (Global Environmental Ethics Council, Clayton): I wrote a book on labeling issues and so I just wanted to correct points made by Greg Jaffe. Connecticut is likely to sign. The other two up in that part of the world, Maine and Vermont, are stuck at the house level where a lot of these bills die; the Senates and governors may not comply. Alaska is labeling only fish and there aren't any GE fish so nothing will happen in Alaska until the FDA finally gets off its butt. Thanks.

Chris Wozniak (Environmental Protection Agency, Washington, DC): A question specifically for Dennis Gonsalves although Tony Shelton certainly could address it as well, or Roger Beachy. The point was made earlier on that the technology is there for a lot of these specialty or minor crops to reach their full potential in the marketplace. The transformation techniques are in place; that's not an issue. Traits are available. Promoters are available. Yet we still don't see a lot of these on the market. We see virtually none. You pointed out that, in your development of papaya, things went fairly straightforward. We do, in fact, have European plum with plum pox resistance registered by an ARS scientist, Ralph Scorza, who did the regulatory work on his own. My question to you is, if the technologies are in place and we see that the regulatory system seems to have worked here, then what is holding it up? Or is it the regulators and these were just two anomalies?

Dennis Gonsalves: This was back in the 1990s—actually the process that we went through was pretty straightforward. We didn't do anything that was out of the ordinary. My personal bias is that a number of people are rationalizing themselves from moving forward and, you know, with the papaya it wasn't so much about whether we were going to make money. As public-sector scientists, our goal was to help. We got no support from the industry—they don't make much money. It did not cost that much. It was almost like getting a series of grants. So, to answer your question, I think some people are gun shy.

Craig Nessler (Texas A&M AgriLife Research, College Station): There's a big difference between deregulating coat protein or another known protein from a foreign protein. The allergenicity questions have been raised but I don't know that they are legitimate. Now you can just use RNAi—you don't have to express the protein at all—which may influence the speed of deregulation. Animal tests on safe proteins from other plant species will still have to take place.

Gonsalves: We went through Japan—people will say that it's the strictest country—but they never required us to do animal tests. They were concerned about allergenicity, food safety, we had to do a lot of bioinformatics, and we had to do gastric juices tests, which are pretty simple. But they never required animal-feed tests, perhaps because it's very difficult to draw firm conclusions from such studies.

Roger Beachy (Global Institute for Food Security, Saskatoon): Dennis or Tony, have you ever worked up the numbers for what it would cost if you needed to do each of these per Craig's suggestion? Have you gone through what it would take to register a product that requires animal testing and a lot of the environmental tests that are now sort of expected for all crops? Do you know what that number is? Chris, maybe you could clarify what it takes to deregulate something novel? Not another Bt, not from RNAi, but from something else? Or maybe someone at a private company can provide an estimate.

Wozniak: I'd like to clarify that question because this is something we've tried to address before. As you probably know, Nick Kalaitzandonakes, in Missouri, has some pretty good data, but even he will admit that a lot of the information that is put under the heading of "I had to do this to get this registered or deregulated" are really things the company would do themselves anyway for their own peace of mind. Remember that even though—as Greg pointed out—the FDA system is voluntary, the onus is still on the person entering the food or feed into the marketplace for its safety. They are personally responsible for that. So, even if you had no regulation and you were putting out, say, a *Bt* corn, or whatever, are you telling me that you would never do an animal-toxicity test? If you have capital investors putting millions of dollars into a large company, for their own peace of mind they would want to know, "Is this going to be an allergen?" "Can it be a toxin?" Some of these tests are expensive, but some of the allergenicity checks can be done on your laptop in 30 minutes.

Beachy: We are talking about specialty crops that have markets not in the hundreds of millions of dollars. We are talking about markets that are considerably smaller.

Wozniak: Right, and I will address that in my presentation, but the real difficulty for me is coming up with that number. If you look simply at the tests that are sort of mandated—and Dave Heron can also address this from APHIS's standpoint—you could go to the third-party laboratories and get their costs for doing the tests and you could also get all the background information that isn't a data generation kind of test, plus the consultants' fees. You could do all that and put this all into the proper format, and come

up with a realistic number. But the numbers I have seen to date, from Nick for example, 10, 12, 14 million, I think are way off base. I don't know if Dave Heron is here, if he wants to try to address that from the APHIS standpoint.

Beachy: It would be really interesting exercise to have that done from the Canadian side and the US side, because the Canadian process is built on food safety. That is their benchmark for release or not. It would be nice to have that available for those in the public sector and land-grant institutions—to say, this is what it will take to release a new pepper, or whatever, to farmers. If that number is a high hurdle, what is that hurdle that we have to overcome? What is the role of the experiment station? Or the state? Or the farmers, in helping it happen? In Canada, the farmers take an active role in support of research. Including developing varieties—farmers pay. Maybe the time is ready for us to do things in a different way and realize that those who will benefit—the farmers—will pay for product development. Maybe their royalty stream will be lower, whatever the number, but think of it differently. We ask about how we move it forward; maybe this is in the mix. Because, right now, it seems that we don't have a sense of what it's going to take to get a new product out. It's a barrier even to getting experiments done. We could just do it by mutagenesis and work for 10 years to get it finished.

Wozniak: Well I have some things to present, some things where I think you can mop up the corners a bit.

Gonsalves: We had a conference a while back at the University of California, where we asked the same question about specialty crops. My thesis is you've got to get other crops of this size commercialized, so people get used to it. Even if you lose money on it. I told the University of California, maybe the dean should contribute \$200,000 to \$300,000 to get a technology like virus resistant, or whatever, that is already developed, then get a sociologist to do the work to get it deregulated and commercialized. Then you actually can analyze the philosophy, the whatever it takes, because it takes actually doing it before you know how to go. With Japan, a lot of it was when to argue and when not to argue. You just got to do it and then you can get numbers. But, if you don't do it, then nothing happens. Like I said, there is no reason I should be talking at this conference. We did this in 1998—my goodness, there should have been other crops commercialized since then.

Wozniak: I'm waiting for that Roundup Ready tomato.

Alan McHughen (University of California, Riverside): When Dennis and I took our products through regulatory approval back in the mid and late 1990s, the costs were not outrageous. As Chris suggested, most of the information required by the regulators were data points that we would have measured anyway just in our regular due diligence, looking at allergens, looking at anti-nutritional factors that are naturally occurring in that food product in the first place. So we had the majority of the data already. The additional cost over and above the cost of doing that due diligence was relatively affordable. Frustrating sometimes, but certainly affordable.

Session 2: Case Studies

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Orange Juice: Will it be Available to Drink in the Future (Agriculturally or Commercially)?

RICKE KRESS

Southern Gardens Citrus

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Southern Gardens is a wholly owned subsidiary of the US Sugar Corporation, with three orange groves located in southern Florida, near Lake Okeechobee, where we have a 20-million-box capacity processing operation (Figures 1 and 2). In a given year, we squeeze 10% to 15% of all the oranges grown in Florida: 25,000 oranges a minute producing 600,000 gallons a day. We store the juice in million-gallon tanks of which we have 56 that we turn twice a year.

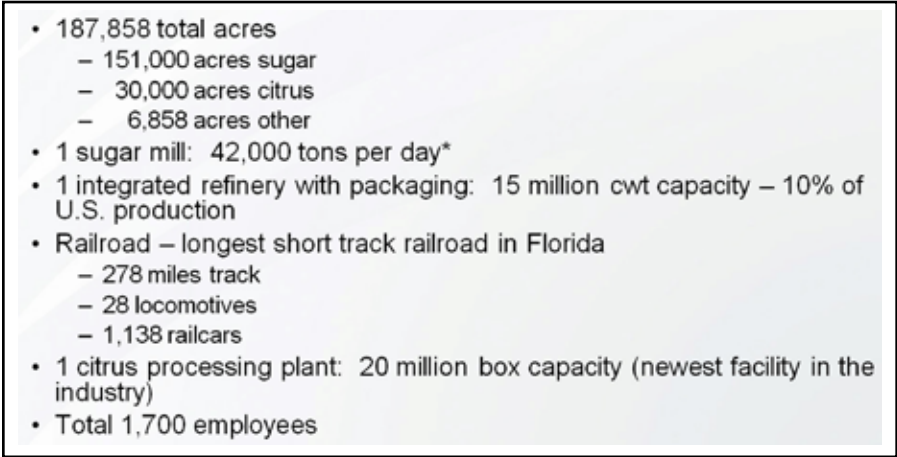
- 
- 187,858 total acres
 - 151,000 acres sugar
 - 30,000 acres citrus
 - 6,858 acres other
 - 1 sugar mill: 42,000 tons per day*
 - 1 integrated refinery with packaging: 15 million cwt capacity – 10% of U.S. production
 - Railroad – longest short track railroad in Florida
 - 278 miles track
 - 28 locomotives
 - 1,138 railcars
 - 1 citrus processing plant: 20 million box capacity (newest facility in the industry)
 - Total 1,700 employees

Figure 1. Corporate assets of the US Sugar Corporation.

CITRUS GREENING (HLB)

Citrus greening—an insect-vectorled bacterial disease, also known as huanglongbing (HLB)—was first detected in Florida in 2005 on the heels of the citrus-canker eradication program, which elicited a widespread aversion to tree removal. After a 2009 study, the National Academy of Sciences identified citrus greening as the most serious disease challenge they had ever reviewed (NRC, 2010).



Figure 2. Southern Gardens citrus-processing plant.

Figure 3 shows the symptoms: yellow shoots, mottled leaves and dead trees. Mineral and nutritional deficiencies, and so on, can produce similar symptoms (Figure 4), which creates a problem.



Figure 3. Gross symptoms of citrus-greening disease.



Figure 4. Nutritional/mineral-deficiency symptoms.

The fruit is misshapen, normally smaller—operative word “normally”—and more and more mature fruit are showing infection (Figure 5).

Figure 6 illustrates the challenge of finding early symptoms. The insect carrying the pathogen—*Liberibacter* spp.—is as prevalent in Florida as the mosquito. When it feeds on an uninfected tree, it can be up to two years before the tree has symptoms.

In October of 2005, we owned one of two commercial groves in which the disease was confirmed. Although we knew little of the disease, we had to be as proactive as possible. By January of 2006, we were in Brazil where the disease had been diagnosed 18 months previously.

The state did a sampling to identify where the disease was in Florida. Figure 7 shows the progression.

Today, every citrus-producing county in Florida is infected. Figure 8 illustrates how rapidly it has spread through one of our groves; each block is 10 acres, and each spot is a GPS coordinate of a tree that was identified as infected and removed. To date, we have lost 30% of our acreage. We are the largest grower and processor of oranges in the state that is vertically integrated. We have identified in excess of 700,000 trees that are infected by this disease. Figure 9 shows the level of infection in Florida through 2011. The data apply through 2011 because, basically, the industry has quit tracking the progression of the disease. We can say, with reasonable certainty, that the infection rate is 100% in the Florida citrus industry; not every tree is infected, but 100% of the groves are infected.



Figure 5. Fruit symptoms of citrus-greening disease.



Figure 6. Symptoms in the grove.

BEST PRACTICE

This disease has been in the citrus industry for years, in the Far East and elsewhere. The program that everybody started to follow was to inspect groves frequently—four times per year—aggressive roguing of infected trees, and full-time scouting for the Asian citrus

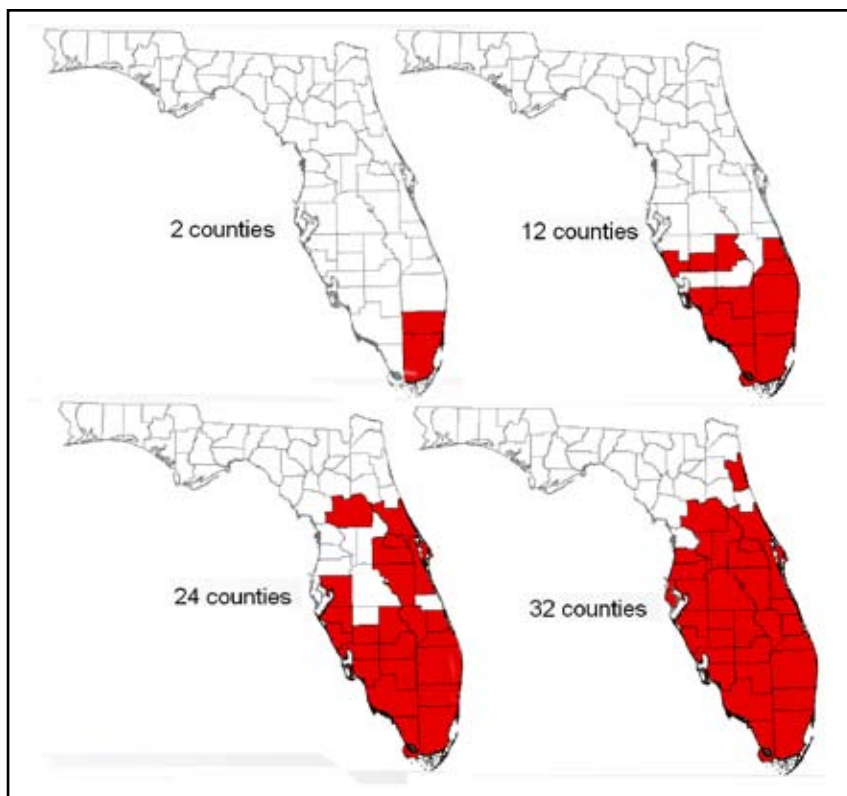


Figure 7. Spread of citrus greening, October 2005, April 2006, January 2007, to June 2007.

psyllid, *Diaphorina citri*, the vector. The industry is working hard to control the psyllid with aggressive applications of insecticides; however, we have learned that tolerance for the insect is less than zero. You have to assume it's there. If you do nothing until you find it, then it is too late. Our growing costs have risen by over 40%, whereas our juice prices haven't gone up by 40%.

CHALLENGES

Should different strategies be chosen in high-inoculum-load areas in comparison with low-inoculum-density areas? Such decisions have to be made "on the fly" and on a large scale. Relevant questions are:

How long will a grove remain economically productive after the disease is detected?

Will replanted groves be disease free? If not, is there a time horizon or will the disease be there forever?

At which point should nutritional approaches be tried?

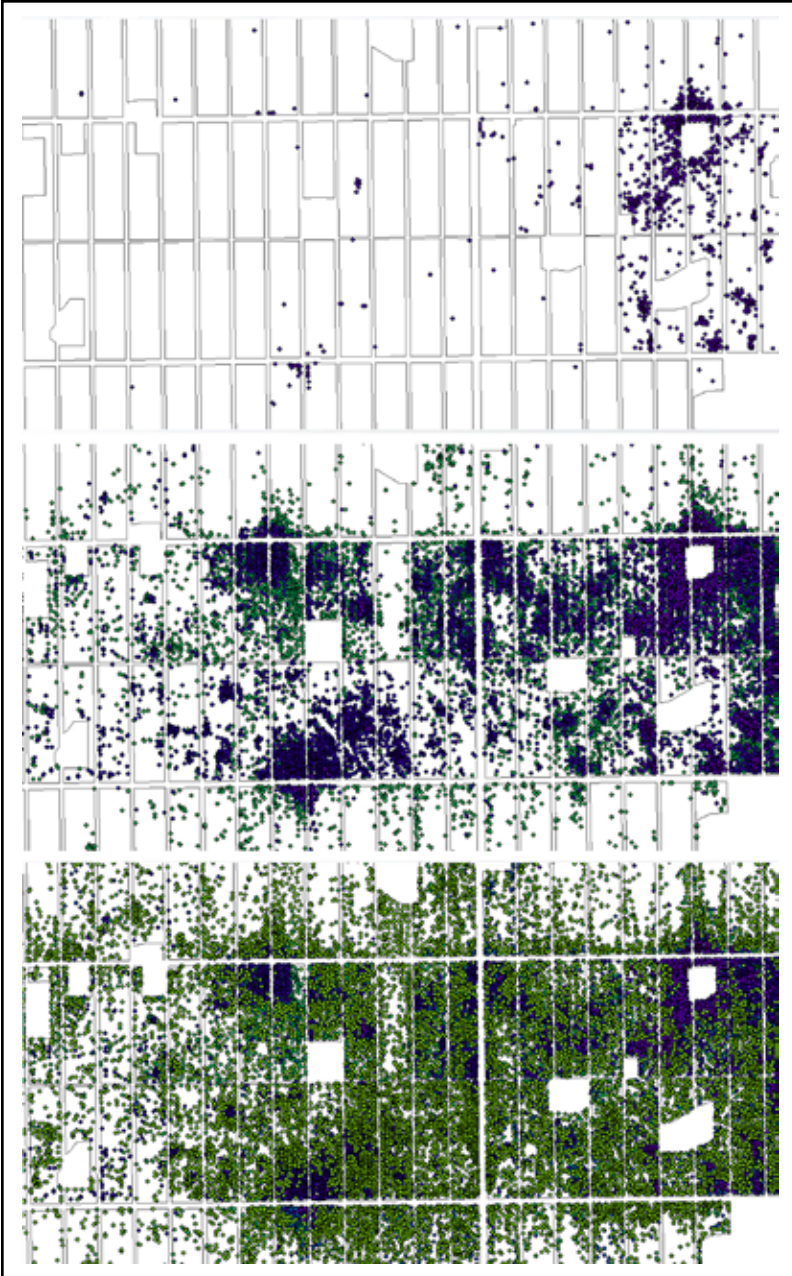


Figure 8. How rapidly does citrus greening spread? Top, Oct. 2005–Mar. 2006; Middle, Oct. 2006–Mar. 2007; Bottom, Aug. 2007–Oct. 2007.

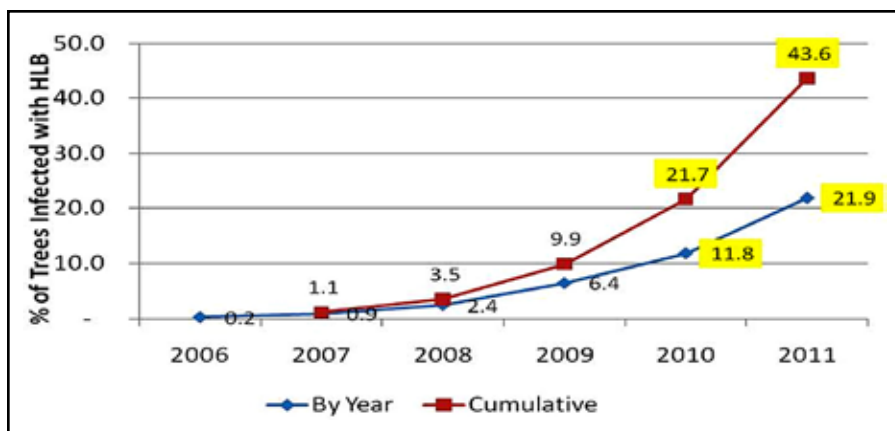


Figure 9. Estimated percent of trees infected statewide.

NUTRITIONAL APPROACHES

Nutritional approaches have been adopted on the basis of anecdotal evidence. There are many such programs, most of which are combinations of foliar nutritional applications, phosphorous acid, and compounds that are thought to be elicitors of systemic acquired resistance.¹ The goal is to maintain the productivity of existing trees. After spraying, the leaves absorb the nutrients and often look more healthy with less dieback. However, where these approaches have been tried in the past—in China and South Africa—they have not been successful over the long term.

Nutritional approaches cost more than pre-HLB growing costs, but less than psyllid control and roguing. On the other hand, the increased costs involved in nutritional approaches may be offset by circumventing scouting for psyllids and tree removal. But, whether using nutritional approaches or not, most growers are still attempting to control psyllids.

A major concern is that these alternative approaches are “forever” in that they involve acceptance of 100% infection, begging the questions of whether replanted young trees will grow and produce under high inoculum load and of how long the time horizon is until recovery is achieved. If psyllid control/roguing is chosen, the nutritional approach can also be employed later, but not the other way around.

WHERE ARE WE?

There are 8,000 citrus growers in Florida. Roughly 50% of the acreage is controlled by about 100 growers. A lot of the production is by small-area growers. There is consensus that the current losses result from HLB infection—with contributions from environmental stresses—and that the losses will continue to worsen. Initial replanting efforts have resulted in high levels of infection within 5 years, with no gain from nutritional approaches. Many groves—even those on nutritional programs—are beginning to decline.

¹Analogous to the innate immune system in animals.

Some 15% of the Florida crop was on the ground in June 2013. If that's a trend, what losses will occur in 2014? Initial replanting efforts have resulted in high levels of infection in less than five years. In a newly planted 40-acre plot, we found 26% infection within 18 months. On the other hand, that was before we realized that the tolerance for the psyllid had to be less than zero.

The solution to this disease, will involve four concurrent processes:

- Research
- Regulatory approval
- Horticultural/agricultural production
- Consumer approval

They have to be tackled at the same simultaneously, because we are not dealing with a corn plant, we are dealing with a tree. When we have the solution, we must be in a position to commercialize it immediately. Several relevant research programs are in progress:

- Disease-resistant plants
 - Texas A&M University
 - Integrated Plant Genetics, Inc.
- Insect-resistant plants
 - Cornell University
- Identification of synthetic resistance genes
 - AgroMed LLC
- Gene delivery
 - University of Florida
- Screening of potential genes.
 - USDA

The major focus of the research is at Texas A&M, on the development of a disease-resistant tree. A second similar project is in progress at IPG, based in Gainesville. Development of an insect-resistant tree may be assisted by synthesis of resistance genes for which several delivery systems are being investigated. The research projects are at varying stages of completion; some are close to the identification of a commercial product. When we find the solution, it will be good for the industry as a whole; Southern Gardens will not monopolize it.

GAINING DEREGULATION

We are working closely with the federal agencies and have had multiple consultations since August 2006 with USDA-APHIS, EPA and FDA. The solution will involve a plant-incorporated protectant (PIP), therefore approval will be needed from all three agencies. With respect to the research here at Texas A&M, we will file for an experimental use permit (EUP) with the EPA as soon as possible.

An important question is, *How do we challenge the solution?* We have developed a rapid screening technique to identify resistant plants. In a greenhouse, plants grown under

optimal conditions are exposed to infected psyllids. Susceptibility to disease is identified within 8 months, significantly more quickly than can be achieved in the field. Plants that appear to be disease-resistant in the greenhouse are then evaluated in regulated field trials. This confirmation of resistance is the first step towards commercialization, then we have to work through regulatory approval of the technology, for which it is necessary to generate a significant amount of data to satisfy all of the requirements of USDA, EPA and FDA to prove that the product is safe. We are working through that process.

Figure 10 provides a summary of what we expect to have to do; these tests are projected to cost in excess of \$3 million. Multiple other aspects come into play. For example, three law firms in Washington, DC, are working with us on this process. It is important to remember that we are not a multinational company. We're a grower/processor, working with a network of people.

Study	Cost (\$1000's)	Study	Cost (\$1000's)
Recombinant protein production	300	Thermolability + in-vitro digestibility	100
Antibody production	100	42-day broiler	150
ELISA method development	100	90-day rat feeding (full tox profile)	275
ELISA Validation	125	90-day rat feeding - China (full tox profile)	75
Western method development	50	Human health risk assessment	50
Composition/Expression/ Agronomics	500	Protein equivalency – recombinant v. plant-made	75
Southern blot	100	Non-target organisms and ecotoxicology	200
Sequencing	125	Honeybee toxicity	30
Within generation analysis	100	Non-target risk assessment	50
Efficacy	200	Product characterization (gene description, transformation, etc.)	25
Inheritance	50	Event PCR method	200
Acute oral mouse	100	Certified ref. materials (EU)	115
Aa homology search	50		
Toxin homology search	50	Total	3295

Figure 10. Summary of likely regulatory strictures imposed by EPA, USDA and FDA.

CONSUMER ACCEPTANCE

After the regulatory process is completed, we must ensure that the consumer accepts the product. As of today, our research indicates that the HLB greening disease cannot be solved without genetically engineering the tree. If citrus-greening resistance were to be obtained with a human transgene or one from a crab or a pig, the orange juice would never make it to the supermarket shelf. Even though the two genes being transferred to citrus are from spinach, the disease-resistant product will have to be marketed carefully.

Orange juice is in an interesting category. It's akin to "motherhood," so education will be fundamental to gaining consumer acceptance.

BENEFITS

The first and most important benefit is that the orange juice industry will survive in the United States. Although the Brazilians have the same disease, they have different regulations and larger growing areas, and they believe they can survive. Another major benefit will be the elimination of the insecticides now being used to control the insect that vectors the disease from infected to healthy trees. At this time, our groves are, essentially, insect-sterile because of the chemicals that we are applying to control the insect. When our genetic solution is put into practice, the impact on the environment will be huge.

THE FUTURE

Our task is daunting, but we have a good approach and our data show that we have good potential for resistance to citrus greening. On the other hand, at our present rate of progress, resistant trees may not be commercialized until 2019, which is not acceptable.



Figure 11. Typical fruit drop in 2013.

We must somehow speed up Mother Nature. If this year's fruit drop (Figure 11) is an indication of what's coming—if we lose 15 percent every year—we could lose the orange-juice industry. Texas and California are watching closely. California's challenge is more pressing because they produce fresh fruit. In Florida, we blend juice, whereas California cannot offer an infected orange for eating. Also, virtually every backyard in the state of California includes citrus trees, which will add to the difficulty of disease control.

It's a daunting task, but we've got an end goal in sight. Orange juice is not going to go away. Florida fruit is not going to go away. No other citrus-growing region can compare to Florida quality, day in and day out. But we have a significant job to do going forward.

REFERENCE

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RICKE KRESS is president of Southern Gardens Citrus, a subsidiary of the US Sugar Corporation located in Clewiston. It is one of the largest growers of oranges in Florida and a major supplier of not-from-concentrate juice to the major brands and private-label grocery trade

in the United States.

He graduated from Cornell University in 1973 with a BS in food science. His industry experience includes Libby's, Nestlé, Seneca Foods, and Northland Cranberries, Inc., in a variety of senior management positions from agriculture to sales and marketing.

Mr. Kress moved to Florida in 2005 to join the Southern Gardens Citrus management team. His arrival coincided with the occurrences of the current citrus-industry diseases, canker and greening. Southern Gardens Citrus and US Sugar have taken a proactive position in working with all factions of the state of Florida and the worldwide citrus industry in efforts to understand and deal with these disease challenges.

He serves on the Cornell University Institute of Food Science Advisory Council as well as the New York State Agricultural Experiment Station Advisory Council task force and is a past president of the Juice Products Association and Processed Apples Institute. Currently, he chairs the D. Glynn Davies Juice Products Association Scholarship program.

Biotech and Apples: Why They Fit

NEAL CARTER

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Okanagan Specialty Fruits is a company of seven people, not much different from many labs in the publicly funded sector. Our lab is in Saskatoon, and, amongst the seven motivated, highly trained staff, we have a research team, we have a marketing director and a communications person, and myself running around like a chicken with its head cut off.

The Arctic apple is our platform project. We wanted to get involved in increasing apple consumption and one way to achieve this was to get them used more broadly, particularly when freshly cut. The Arctic apple has no polyphenol oxidase, the enzyme that drives the browning reaction; it is truly non-browning. Other apples that don't turn brown within six hours are referred to as low-browning, a consequence of substrate deficiency, not lack of the enzyme.

We are often asked, "Is Arctic a new variety?" No. We can do this with any variety. We did it first with Goldens and Grannies (Figure 1), which are now in the hands of the regulatory people. We have done it also with Gala, Fuji, McIntosh, Honeycrisp and Jonagold. The trees behave in the orchard exactly like their conventional counterparts, until the fruit is bruised, bitten or cut. They are equally healthy and productive. The apples in Figure 1 were cut several days before. The flesh of Arctic apples dries out before it goes brown.



Figure 1. First non-browning varieties.

Left: Arctic® Golden vs. conventional Golden Delicious

Right: Arctic® Granny vs. conventional Granny Smith

Initially we worked on various projects with peaches, cherries and apples, but soon realized the need to focus. We concentrate on apples, and particularly on the Arctic technology with the objective of making it available to the apple industry as a whole. If Okanagan Specialty Fruits survives commercially, we hope to diversify in due course.

Figure 2 shows that the overall trend in fruit and vegetable consumption has been upwards, with apple a notable exception. The *per capita* consumption of apples has been trending downwards for the past 25 years, which is bad news for growers. The industry maintains current production levels because of increasing population, not because we're exporting more. China, the biggest apple grower in the world, now dominates Asian export markets that have, historically, bought US apples.

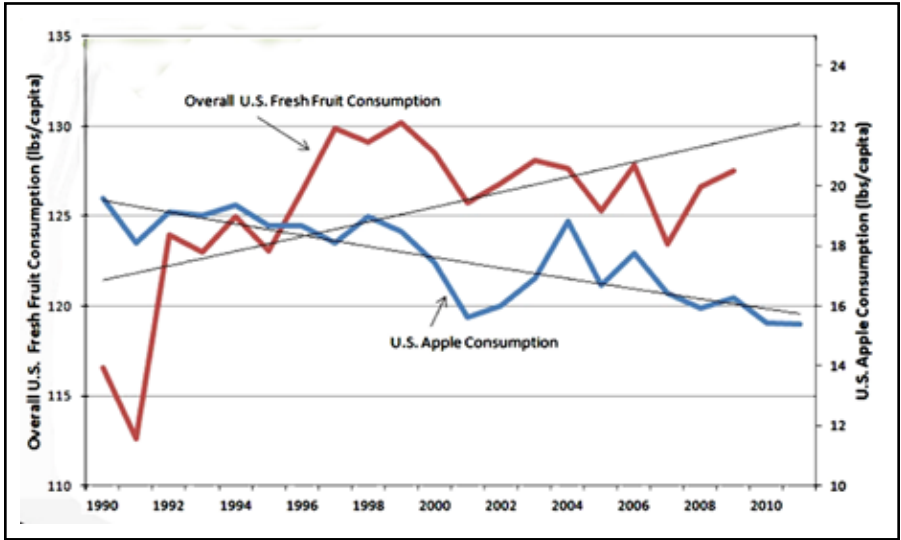


Figure 2. Trends in fruit consumption (USDA Economic Research Service).

What could we do to increase apple consumption? We looked for a consumption trigger, and found one in the fresh-cut carrot model that was introduced in 1988 (Figure 3). Carrots were cut up, tumbled it and bagged, and, by 1997, consumption had doubled. It essentially saved the carrot industry. Before then, they were used as ingredients for soups and stews and rarely eaten raw. The trend has been down since 1997 because of competition from other products, mostly other vegetables. If we could do this with apples, and increase consumption even by 1 lb per person per year, it would be great news for the industry.

SILENCING PPO

RNAi is used to silence the four genes that encode polyphenol oxidase. This is like rerouting ten pieces of track on a railway from Los Angeles to New York (Figure 4). Our vector has approximately 1,800 base pairs and there are 750 million base pairs in apples; it's an exact process.

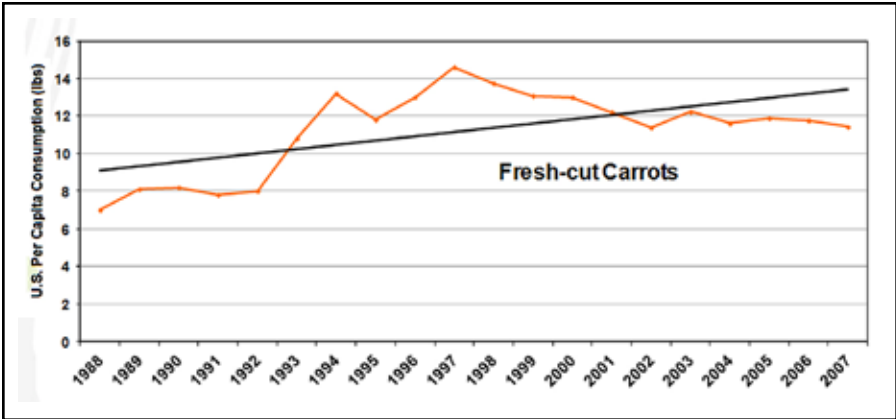


Figure 3. Trend in carrot consumption (USDA Economic Research Service).

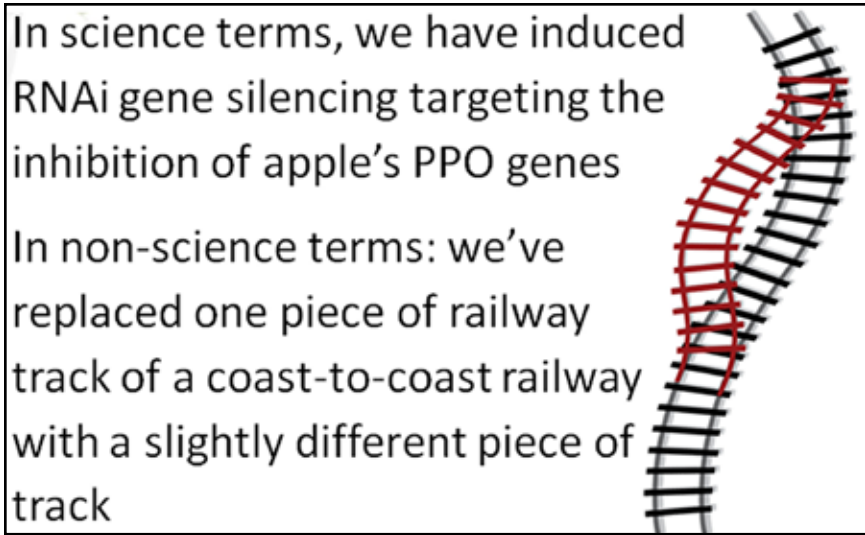


Figure 4. The science is relatively simple.

People ask if browning is an important issue. In fact, browning precludes apples from many potential markets. The need to be treated with an antioxidant to stop browning means that a lot of commercial kitchens won't handle it. It's just too much work.

The control of enzymatic browning in Arctic apples benefits everyone in the value chain. Scuffing that occurs during harvesting and post-harvest handling doesn't show on Arctic apples, thus reducing cullage. Similarly, in the packing shed, handling losses are mitigated. The fact that the juice doesn't turn brown provides opportunities for new products. Because the pulp doesn't go brown, fruit leathers look more appealing. From the grower to the processor (Figure 5) to the consumer, we can identify quantifiable benefits and creative people will find many new uses for these apples.



Figure 5. Fresh-cut apple processors' benefits.

CONSUMER PREFERENCE

What does the consumer think? Every single person in our many focus groups has wanted to try an Arctic apple. Even with those who react initially with, “Oh, no, I only eat organic,” or “Oh, I’d never eat any GM,” 90 minutes exposure to the air without browning results in “Wow, I must try one of these things.”

We surveyed 1,000 self-professed apple eaters, asking, “What’s the likelihood of your buying a non-browning apple?” About 51% said “somewhat likely” or “extremely likely.” So then, against the advice of our consumer-survey company, we said, “A non-browning apple exists and it was developed through genetic engineering.” Positive responses fell from 51% to 49%; we lost 2% when we used the term “genetic engineering.” So then we said, “A non-browning apple exists. It was developed through genetic engineering by using the apple’s own genes to turn off the gene that makes it go brown.” With that half sentence added, it went to 59%—above what it was initially. When asked, “Would you rather eat an apple that is genetically engineered to prevent browning or one that had an antioxidant chemical applied?” two-thirds professed preference for the untreated, genetically engineered slice. Clearly, a little information can go a long way.

Our target is fresh-cut apples in bags, similar to baby carrots. Surprisingly, the whole apple is becoming too big a commitment in the world of texting and smart phones; how do you eat an apple and text? If apples were offered during our coffee break, few would avail themselves:

- What if someone engages you in conversation when you have a mouthful of apple?
- What do you do with the core when you’re finished?



Figure 6. All Arctic apples will be voluntarily labeled.

In contrast, if apple slices were offered, it is likely that they would all disappear.

The fresh-cut opportunity in apples is huge, but the problem is that the antioxidant used to control enzymatic browning is worth as much as the fruit. If we can dispense with the antioxidant, we'll get rid of the citrus-like "buzz" and 40% of the cost. The price break will make apples more accessible for packed lunches and for food-service and many other uses.

LABELING POLICY

Part of our commitment to transparency includes telling people about what they buy. Growers interested in planting Arctic apples will have to agree to apply the sticker shown in Figure 6. It doesn't say "genetically engineered," but it does say "Arctic," and media attention dictates that by the time Arctic apples hit the marketplace, many if not most people will know that they have been genetically engineered. Also, our website details the underpinning science.

FROM THEN TO NOW

In 1996, we formed Okanagan Specialty Fruits to use genetically engineering tools in apple. We licensed a technology from CSIRO in Australia, who had proven the non-browning concept in potato. However, we found that the potato method doesn't work in apple; we had to silence four genes. By 2002, we had it working in the greenhouse (Figure 7) and in 2003 and 2005 we planted field trials in Washington and New York States. We started to build a package of data for regulatory purposes. In the apple business, particularly with plants from tissue culture, there is a juvenile tendency. It is essential to ensure that everything is stable, so, every year, we took buds, and propagated more and more new trees—with larger and larger field trials—and then we started to get fruit from the early trees. We felt that we were getting a properly representative data set.



Figure 7. The path to market.

When we had the data we needed, we embarked on the regulatory process in 2010 (Figure 7), which takes us to where we are today. Hopefully, we are close to obtaining deregulation.

OBTAINING DEREGULATION

I can't provide a firm number for the cost of the deregulation process. A major item is staff time. We spent \$10,000 to \$15,000 on the services of regulatory consultant who made things overly complicated, so we did it ourselves. I don't know whether advice received from the federal agencies in the end helped us or not. The advice from APHIS was "Keep it simple. Don't bring a trailer in here and dump all sorts of data. We want it synthesized and analyzed with good statistics." In the end, we went a little light and

they came back with questions and we had to add more data and more statistics. It was our first time through and we had no benchmarks. We examined other submissions, entailing different crops and different traits, and it was hard to correlate ours with theirs. However, my major comment is that this is doable and it's not exceedingly expensive. It takes time and a lot of frustration, but if you're stubborn and bull-headed, you'll get there. People shouldn't be thinking in terms of millions of dollars. The out-of-pocket component isn't that much.

In Canada we regulate the product, not the process, whereas in the United States, you regulate the process, but the submission materials were essentially the same. In Canada a significant challenge lies in having to submit all three documents at once, related to food, feed and environmental issues. For the United States, we tackled the USDA-APHIS petition first, which raised many questions that got us bogged down. Eventually we submitted the FDA application and the questions coming from APHIS helped us put the environmental document in better shape for submission in Canada (Figure 7).

By now, we had hoped to be in the midst of the second public comment period with APHIS, but we're not. The delay results from our petition being one of eleven. I don't know why they can't be done one at a time, but we hope to be deregulated by the end of the year. In Canada, we are working our way through molecular and agronomic questions with the authorities; we had a constructive meeting with them in April 2013. We expect to provide the necessary information by the end of July 2013, and we have been told that we should be finished in Canada by the end of 2013.



Figure 8. Preparation for commercialization.

COMMERCIAL STATUS

We are talking to growers, industry representatives, retailers, wholesalers, brokers, *etc.*, on an almost daily basis to build industry buy-in. Test blocks have been planted by growers in Canada and United States. Figure 8 shows Arctic trees planted in the spring of 2012 and now 7–8 ft tall (June 2013). They were defoliated in the spring of 2013 to prevent flowering, pending deregulation; they are grown under permit. We are putting trees in the hands of growers so that they can “kick the tires,” and make sure that Arctic trees perform to expectation. We have a fair amount of uptake, but there’s also a lot of pushback. Some growers don’t want to have to go through the unfamiliar permitting process to put in a test block. And then some are concerned about market reaction, and many don’t want to plant until after deregulation. If they plant a 10-acre block and then it’s not deregulated, what will they do with it? On the other hand, if approval occurs according to expected timelines, we will have fruit for test-marketing in 2015.

We are heavily in the educational mode, particularly *vis-à-vis* growers. I have spoken around twice per month for the last two years at conventions, conferences and trade events, trying to educate. For a company of seven people with two involved full-time in education, that’s a huge commitment, but this is what it takes. It’s not about the science anymore and the product is worth the effort, but now it’s about educating. As already stated, a strong focus is on transparency. Only 25% of people have heard of biotech crops, and many people who don’t have a clue are likely to give weight to anti-biotech activists.

Our message is short and sweet: it’s just like any apple; it looks like an apple; it grows like an apple; and it tastes like an apple. It just doesn’t go brown. And, associated consumer benefits can drive consumption, by putting apples in more places and reducing waste in the home.

IMMEDIATE FUTURE

Right now, our lab workers are answering regulatory questions and generating more Arctic varieties. But we are also involved in proof-of-concept work in scab resistance, fire-blight resistance, and storage scald. We have made a commitment that by the third quarter, we will ramp up our research work in those three traits and investigate stacking technologies.



NEAL CARTER is president and founder of Okanagan Specialty Fruits™ (OSF), a biotechnology company specializing in the creation of novel tree-fruit varieties. Outside of OSF, he and his wife, Louisa, grow and pack apples and cherries from their orchard in British Columbia's Okanagan Valley. For nearly 30 years, Neal has worked with numerous crops as a bioresource engineer around the globe, ranging from maize to mango, from growing to harvesting, packing, storage, processing and packaging. It was through this firsthand experience that he was persuaded that biotechnology can help agriculture meet the ever-expanding global demand for food.

The Carters founded OSF in 1996 in order to explore opportunities to utilize biotechnology to boost fruit consumption and sustainability. OSF's flagship project is the development of non-browning Arctic® apples, which have been engineered to resist browning by silencing genes that produce polyphenol oxidase. Arctic apples are currently progressing through the deregulation processes in Canada and the United States; availability in grocery stores is expected within a few years.

With apple consumption flat-to-declining for the past couple of decades, Mr. Carter believes that Arctic apples will provide a consumption trigger for the industry by providing numerous benefits throughout the supply chain.

Bringing Biotech Potatoes to Market

HAVEN BAKER

J.R. Simplot Company

Boise, Idaho

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J.R. Simplot is a privately held \$6 billion company, with 10,000 employees. We mine phosphate and manufacture fertilizers that we sell to farmers. We've been a longstanding potato producer in the United States, and we're involved in livestock. Plant-biotechnology work was initiated in 2001 with a few scientists. Our mission is to create safe, healthy, sustainable crop improvements with a focus on potato. We now number about 65 and are in the comment period for our first regulatory submission. We will petition for our second-generation biotech crop in six to eight months; our objective is to bring multiple products to market.

BUILDING ON BIOTECH

Building a biotech business involves a lot more than science. Certainly, commitment to good science is essential. Obtaining proprietary technology is often a necessary part of R&D. The regulatory side requires submission of sufficient, but not excessive, data. And business development includes determination of the value of the trait in question, and building marketplace acceptance. Potato production involves four sub-industries. Each is large and comprises varied players, therefore good marketing is essential to build general acceptance. The last component is commercialization. It is one thing to obtain regulatory approval, but it takes much effort and many trials to bring farmers along; much more is involved than running regulatory trials for the USDA.

This area of endeavor is not without controversy and your company culture must inculcate willingness to address such controversy with awareness that you won't be everyone's best friend all the time.

INNATE TECHNOLOGY

Our marketing effort involves talking about our Innate™ technology:

An innovative biotechnology approach to improving crops using a process that uses plant genes to enhance desirable traits and reduce less desirable ones.

Innate™ is a way of putting a plant's own genes back into a plant. We needed a way to introduce our biotech approach to the potato industry and eventually to consumers. As part of our market research, we tested several messages and created Innate™ Brand as a face for new plant-biotechnology processes for improvements in crops and foods. Innate™ provided a way to talk about our technology without resorting to the less consumer-friendly terms, intragenic and cisgenic.

We take DNA that elicits either expression of (a) desirable trait(s) or less expression of (a) less-desirable trait(s) from a cultivated variety or from a wild-species progenitor potato, and put it back into Russet Burbank to produce an Innate™ Burbank (Figure 1). This is the level at which we want to communicate the technology, both to growers and to consumers.

MARKET RESEARCH

We've done a lot of market research that shows that results depend on how questions are worded. However, with enough studies, trends emerge. The data in Figure 2 demonstrate potential consumer acceptance of the Innate™ technology—having explained that it is a

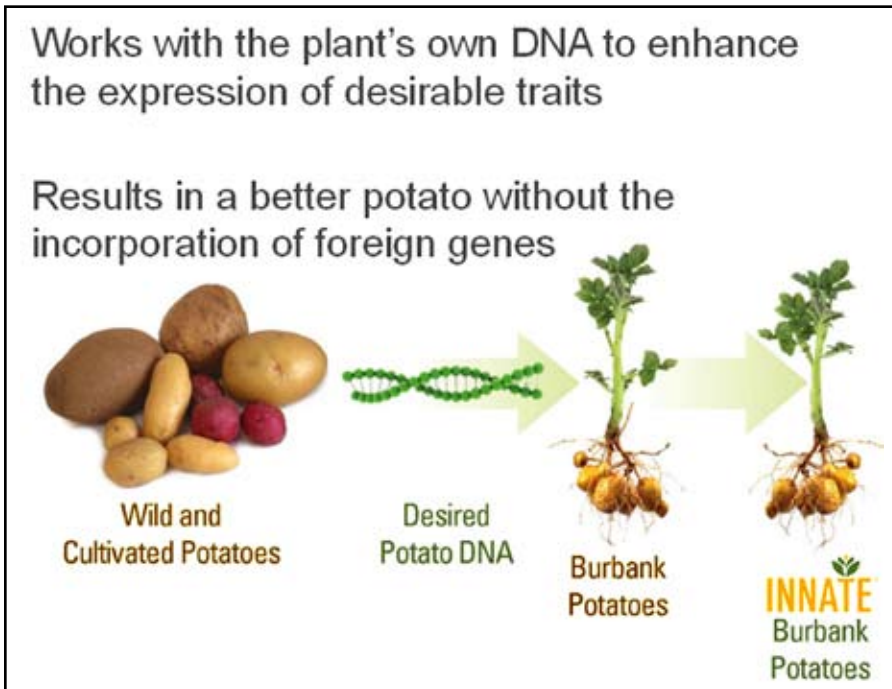


Figure 1. Innate™ technology: How it works.

plant-based gene transfer—in comparison with genetically modified, traditionally bred, and “biotechnology” counterparts. It is noteworthy that use of the word “biotechnology” elicits greater comfort among consumers than “GMO.” Explanation of the Innate technology produced acceptance close to that of plant breeding, but not quite there. Our goal is not to be acceptable to everybody, but to be as acceptable as plant breeding, and, clearly, we are close, which is a promising message for all using molecular genetics for crop improvement, *i.e.* consumer acceptance of the technology is potentially good.

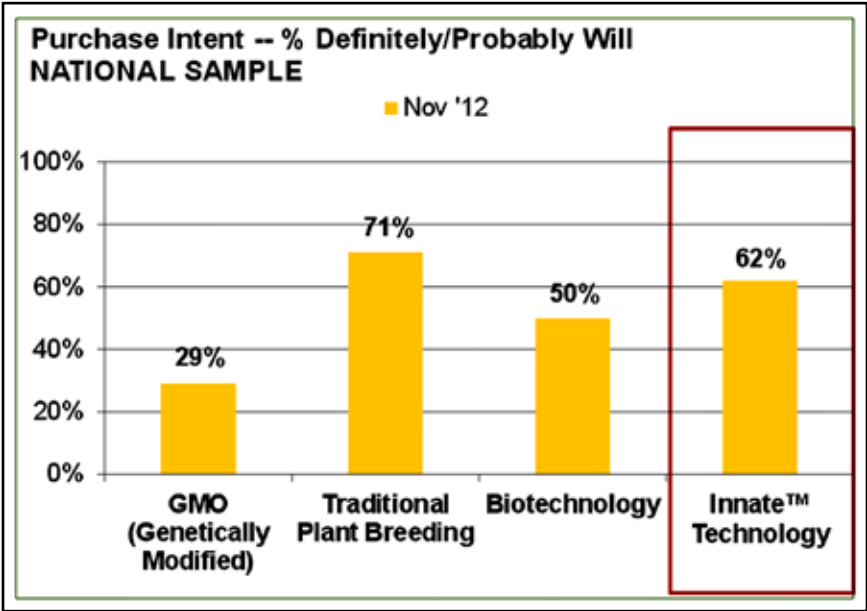


Figure 2. Survey: How likely would you be to purchase fruits and vegetables that are improved using Innate™ technology?

FIRST GENERATION OF TRAITS

Traits we are bringing to market using “Innate 1.0” potato are:

- Reduced black-spot bruise, and
- Reduced asparagine.

Reduced black-spot bruise is a trait similar to non-browning in the Arctic apple.¹ We had to silence only one of the five or six polyphenol oxidase (PPO) genes, PPO 5 in a tuber-specific manner. And we have down-regulated asparagine in tubers—again tuber-specific—by silencing asparagine synthase. Instead of asparagine—a precursor of acrylamide—the modified tuber accumulates glutamine, so the nitrogen content stays relatively similar and yield is unaltered, which was an unexpected benefit. If asparagine synthase is silenced throughout the plant constitutively, growth is compromised.

¹Pages 87–94.

Four varieties have been improved via Innate 1.0: Russet Burbank, Ranger Russet, Atlantic and Snowden. Russet Burbank and Russet Ranger are the primary French-fry varieties, and Atlantics and Snow are the primary varieties used to make chips. The improvements result in benefits to growers, processors and consumers. Browning occurs not only after cutting (Figure 3), but also when stacked in storage, which causes pressure bruising. Usually, tissue change is minimal, but it does occur and is a significant problem in the fresh market. In the French fry and chip industries, brown potatoes are removed and used for cattle feed; the grower is penalized and the processing plant loses productivity.

Acrylamide occurs naturally and is present in almost all baked and fried foods. It forms at around 300°F. California has a labeling requirement for baked or fried potato products containing acrylamide above 300 ppb. In response, some companies mitigate the problem via enzyme use, whereas other companies have withdrawn their products from the market in California. Figure 4 shows that potato chips made with Atlantics accumulated acrylamide at 450 ppb, whereas Innate™ Atlantics contained acrylamide at 130 ppb. Similar patterns were found with French fries made with Russet Burbank and Ranger Russet and their Innate™ counterparts (Figure 4).

Two ingredients contribute to acrylamide formation: asparagine and sugars. We control only the asparagine component in the first generation of Innate™ potatoes, and, in general, we see reductions in acrylamide content of 50% to 70%.

A key ancillary question: *Could the benefit of lowering acrylamide overcome opposition of biotech?*

UNIFORMITY

Those whose job is to improve potatoes, and who are focusing on the farmer, are missing 80% of the potential. Downstream companies that make products from potatoes are the big sellers. Farmers produce \$3.5 billion worth of potatoes every year, whereas somewhere around \$40 billion worth of French fries are sold. The market is controlled by customers who demand uniform quality in their French fries and chips. Figure 5 shows a spidergram containing a 15-point hedonic scale. Innate™ potato products must give data identical to their non-Innate counterparts in terms of performance from a sensory perspective, aroma, crispness, toughness, *etc.* Although we've affected the asparagine content and the PPO, we have not affected starch pathways or other metabolism that affect sensory perception, which is a major consideration for our customers.

Figure 6 shows field data for Innate™ Russet Burbank in comparison with its parental counterpart; these trials are expensive to run. Each comprises an acre or two, and yield-tracking data are generated using modeling software. We've done this a number of times and find consistently that there is no difference between Burbank and Innate™ Burbank (E12), and that's important because some farmers have been led to believe that yield "drag" results from biotech traits.

SECOND AND FUTURE GENERATIONS

In 2013, we are running over 30 field trials across the United States and Canada, including a commercial development trial in Texas. We encourage growers to visit our commercial



Figure 3. Comparison of an Innate™ potato (left) and a traditional potato 10 hours after being cut.

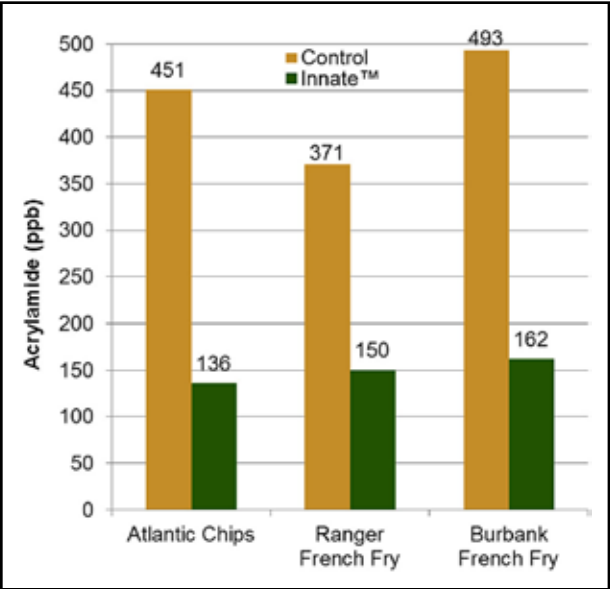


Figure 4. Simplot research, 2012.

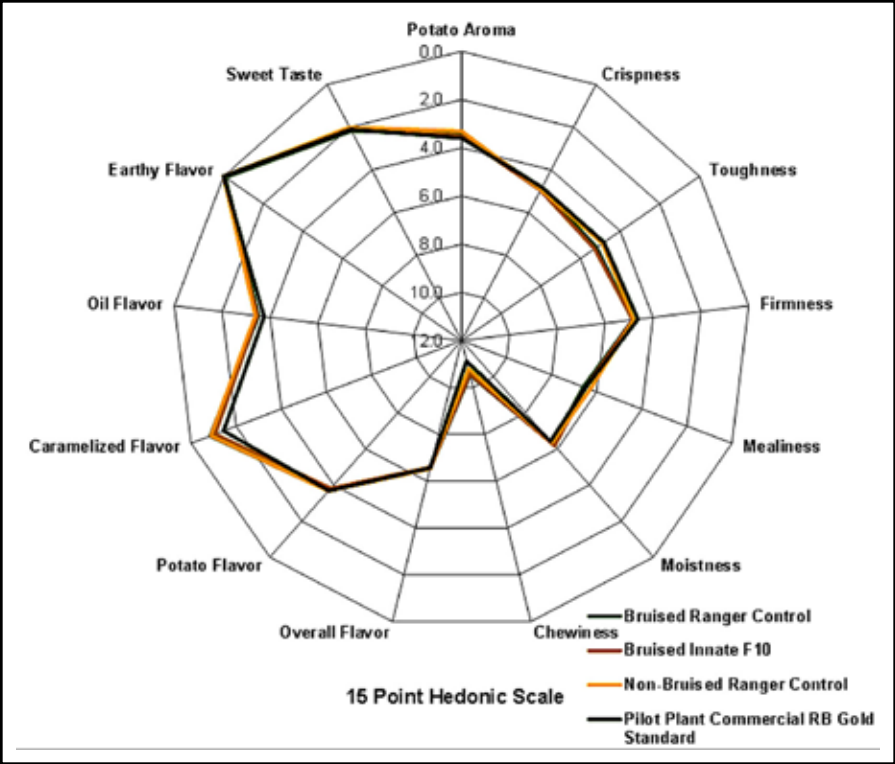


Figure 5. Spidergram: Ranger Russet and Innate F10 Ranger Russet comparisons with Russet Burbank gold standard—no sensory differences.

trials. Also, we have advanced regulatory trials for the next generation of Innate™ potatoes. Figure 7 shows the traits that we are working on.

Generation 1.0 will comprise low asparagine and low bruising as mentioned, and less sugar when harvested. Our projection is to launch Generation 1.0 in 2015. We expect to launch Generation 2.0 in 2017 and, to that end, we are working on a gene that provides sugar control. Potatoes are stored at between 48°F and 52°F, sometimes at 46°F. That temperature is one of the single most important economic drivers in the potato industry. The gene that we’re working on for sugar control allows storage at 38°F, at which several post-harvest issues are circumvented because of less disease. We have licensed a gene from Jonathan Jones’ lab—the vnt1 gene—for broad resistance to strains of *Phytophthora infestans*, which causes late blight. In our research pipeline we are also working on resistance to potato virus Y (PVY), on improvements in use efficiencies of water and nitrogen, on enhanced vitamin content and on improved tuber set.

Figure 8 demonstrates positive effects of the Innate™ 2.0 technology on fresh-potato quality. As a result of storage at 38°F, zebra-chip discoloration (top left), caused by *Liberibacter* spp. is decreased. And dark “sugar ends” (bottom left)—caused by a high concentration of reducing sugars—are alleviated by silencing the gene encoding invertase.

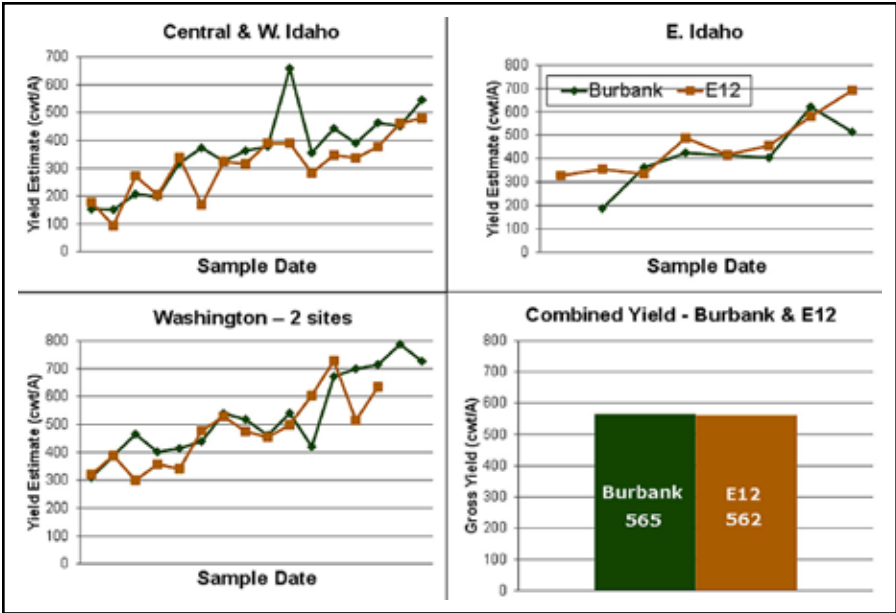


Figure 6. Russet Burbank and Innate™ E12 yield comparisons

Innate™ 1.0 2015 Launch	Innate™ 2.0 2017 Launch	Future Traits 2018+
<ul style="list-style-type: none"> • Low Asparagine • Low Bruise • Lower Sugars at Harvest 	<ul style="list-style-type: none"> • Sugar Control • Cold Storage • Sugar Ends • Late Blight • Low Asparagine • Low Bruise 	<ul style="list-style-type: none"> • PVY • Water Efficiency • Nitrogen Uptake • Enhanced Vitamins • Tuber Set

Figure 7. Future Innate™ traits.

Atlantic is an 85-day potato, whereas most others have a growing season of 110 to 140 days. For this reason, Atlantics are grown all over the world, even though they don't store well; they build sugars too quickly, which causes browning that no one wants. Resistance to browning after six months at 38°F means a lot to farmers (Figure 9). The 25,000 thousand acres of Atlantics that are grown in the United States must be shipped to processing plants a day or two after they are dug. The Innate™ technology will expand the acreage of this variety relative to a number of others.

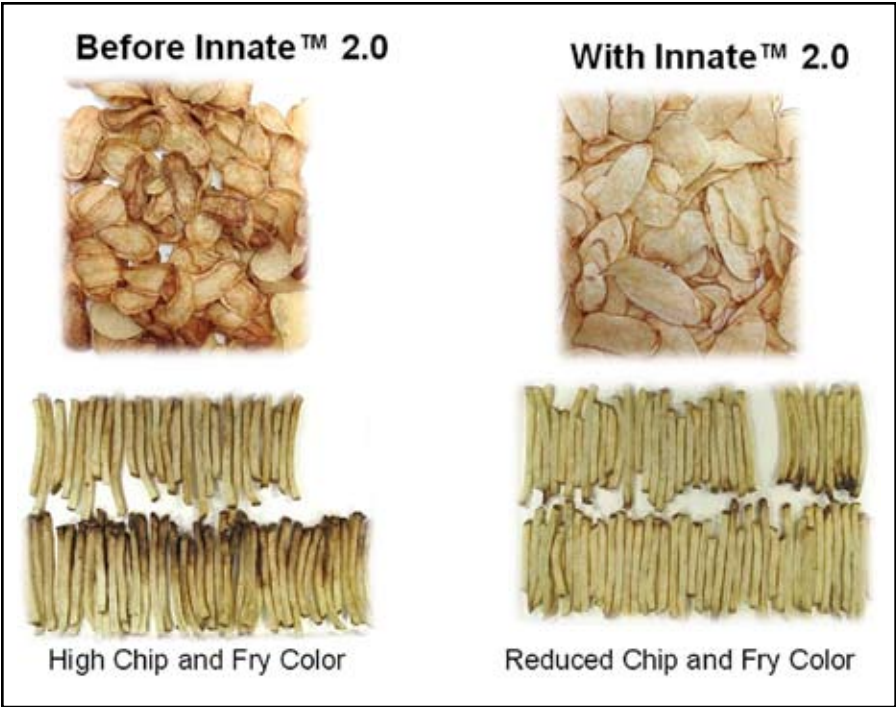


Figure 8. Innate™ 2.0: Impact on fresh-potato quality.

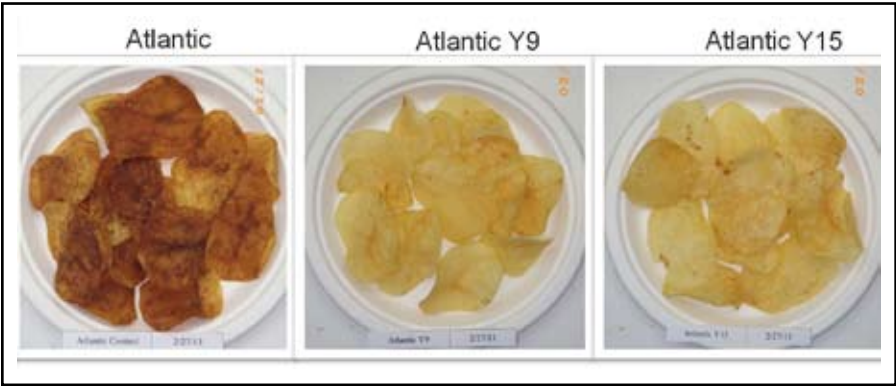


Figure 9. Innate Atlantic 2.0 lines Y9 and Y15 fry with reasonably good color after six months of storage at 38°F.

REGULATORY AND BUSINESS CONSIDERATIONS

If you create a new potato through biotechnology, using only potato genes, how are you regulated? If you used agrobacterium, you’re regulated by the USDA. If you have a novel trait, you’ll be regulated by Canada, and if you use recombinant DNA, you’ll be regulated

by Japan. Whether the technology is cisgenic or intergenic, it will be treated the same as GM in Europe. New TALEN^{TM2} technology has exciting potential, but it is possible that deregulation will be needed to protect export markets. We believe that, over the coming 25 years technology improvement will move back in the direction of transgenics, having used within-species manipulations to gain consumer acceptance of genetic approaches. Although we are committed to our InnateTM technology, we keep an open mind and avoid disparagement of other technologies.

Figure 10 represents our projected regulatory timeline. At this point, June 2013, we are in a public-comment period from which we expect deregulation of Innate Russet Burbank 1.0, Innate Russet Ranger 1.0 and Innate Atlantic 1.0 in 2014, and that these three products will be on the market in 2015. If we are lucky, InnateTM potatoes from the 2014 growing season will be included as ingredients in products available to consumers in 2015. In 2016, we expect deregulation of InnateTM 2.0 products, with commercial introductions of Innate Russet Burbank 2.0 and Innate Ranger Russet 2.0 in 2016 and 2017, respectively. Deregulation of InnateTM 3.0 technology will be applied for in 2018.

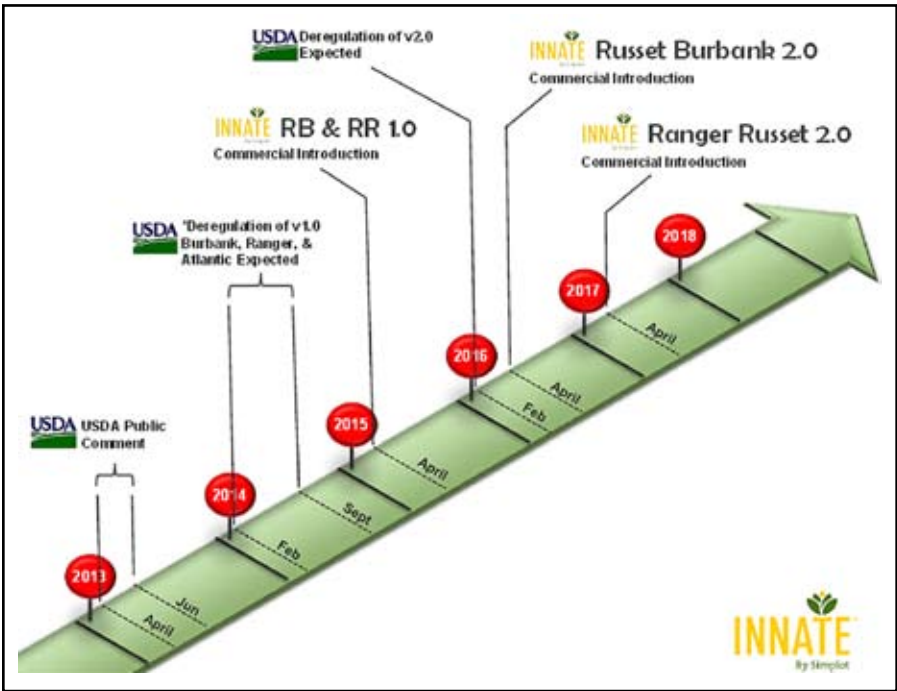


Figure 10. InnateTM timeline.
(*There is no guarantee that the USDA will deregulate InnateTM potato products.)

²Transcription activator-like effector nuclease.

IDENTITY PRESERVATION

From the point of view of identity preservation, potatoes have important inherent advantages:

- Potatoes are largely self-pollinating. The flowers have no nectar, and are not visited by insects. Separation by 20 m is sufficient to eliminate the risk of outcrossing.
- Potatoes are clonally propagated from tubers, not grown from seed.
- Lines can be easily distinguished with PCR.

BUSINESS CHALLENGES

The potato market comprises several segments:

- Chips,
- Frozen products (French fries and hashbrowns),
- Fresh potatoes, and
- Dehydrated potatoes.

Each of these entities is supplied to the consumer as different varieties by separate industry players. Satisfying the needs of producers presents a challenge to the potato supplier. Regulatory approvals *vis-à-vis* international markets represent another challenge. The capital that needs to go into seed potatoes is another issue. The value of US potatoes at the farm gate is \$3.5 billion, which represents an initial investment of \$350 million. Seed-potato cost runs at \$400 dollars per acre if not more, which is expensive.

Another issue is the variety of varieties. With eight varieties, we believe that we can capture 60% of the potato market. To get to 90% would require double that, and, since backcrossing is impossible, each event has to be deregulated. Of course, it will be impossible to capture the whole potato market. Our goal is to capture the majority of the chips and the frozen and fresh markets; we expect to leave specialty potatoes to competitors.

Another challenge is the traditional business model for biotech (Figure 11). Critical aspects are how much the trait improves the crop and market penetration, *i.e.* how many acres; those two are multiplied together to calculate the revenue. If the crop is improved by \$100 dollars an acre, the grower nets \$66 and we get \$33. The problem with specialty crops is that few traits are available that will pay back the investment. In potato, there aren't many \$300 or \$400 traits, and a \$100 trait won't pay the bills.

Traditionally, with row crops, new varieties were produced by plant breeders—mainly at the universities—which seed companies multiplied and sold (Figure 12). Farmers planted them, and the produce became widely available. In the biotech industry as soon as a stable transformation is achieved, breeding is initiated to put the trait into appropriate germplasm; accordingly, genetic manipulation, breeding and seed dissemination are now united in one entity, usually achieved through acquisitions. Like the traditional way, the biotech product then goes to the farmer, and then it goes worldwide.

With potatoes—and probably a few other crops—the farmer, the food processor and the food processor's customers are vertically integrated (Figure 13). Accordingly, 95% of the potatoes that are planted for the French fry industry are contracted by the food

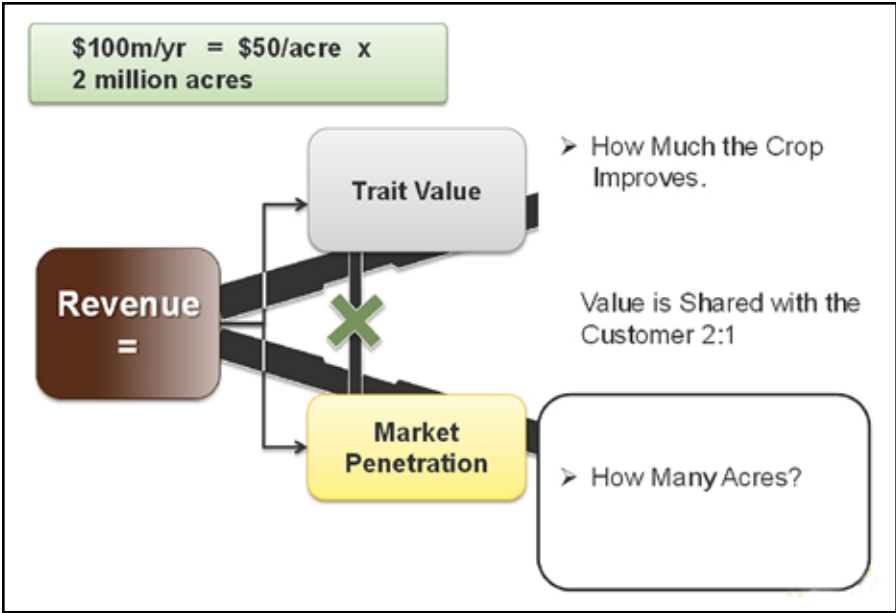


Figure 11. Revenue model for the biotech industry.

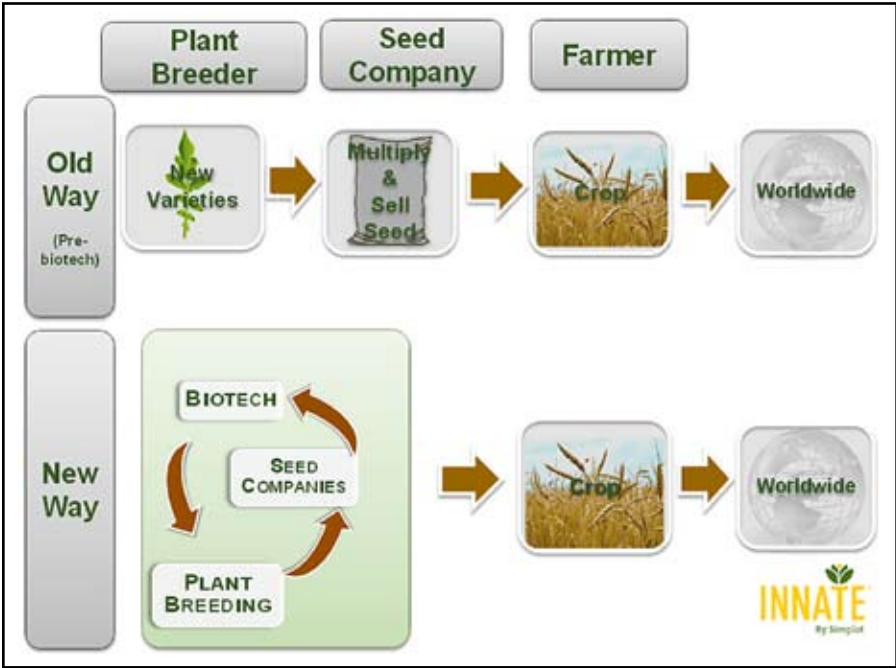


Figure 12. Crop development.

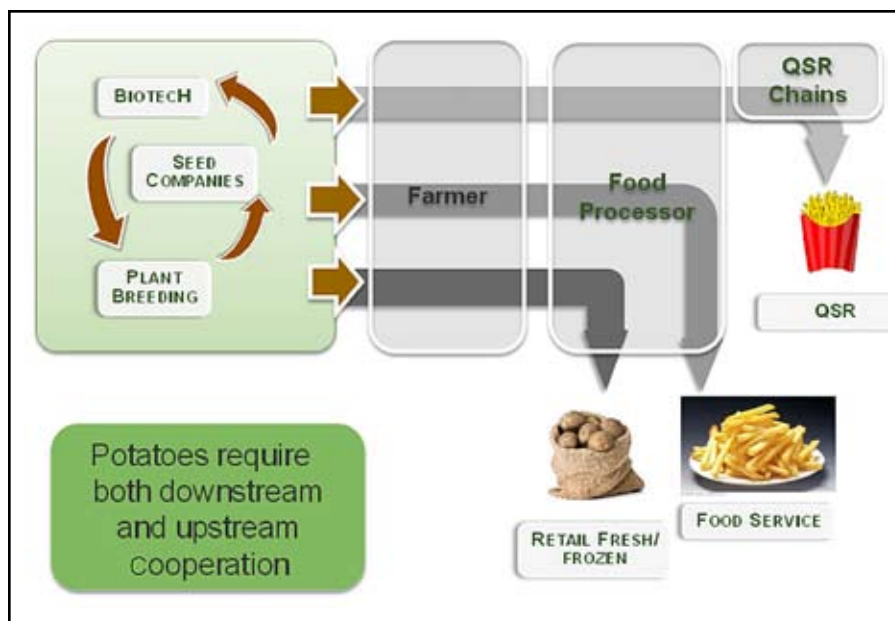


Figure 13. Potato commercialization.

processor. The food processor tells the farmer which variety to buy, and, if the quick-service restaurant (QSR) chain is large enough, it tells the food processor which variety to make French fries with.

These three entities operate in unison, so if a new variety is to be introduced, all three have to be lined up, or markets must be found where at least the food processor and the farmer can line up. Fresh and frozen present those opportunities. And food service is another. Customers sometimes aren't picky, so achieving that alignment may be harder than it sounds.

FINAL THOUGHTS

We have found the number of traits that are gene-silencing based, which should mean a less complicated regulatory package. In terms of reducing expense, not introducing a new protein is a significant advantage.

Another thing we have found is that the traits aren't always obvious. It took us a couple of years to fully understand the benefits of the low-sugar trait and its economic implications. It was necessary to store potatoes for 6 months and then make fries or chips.

A tricky point: the black-spot bruise trait benefits growers, and that benefits processors, which benefits the consumer. It's win-win-win. But it presents a challenge in terms of who pays. Presumably it's the farmer, who must get some of that money from the processor, who then must restructure the contracts with reluctant farmers. Calculating value thus becomes problematic.

Lastly, it can take a while to structure relationships and get people comfortable with biotech. On the other hand, after they're comfortable, we've seen significant support. We're in a comment period now, and 80 comments have been received, of which probably 25 are positive, a lot of them from growers. We are excited about that.



HAVEN BAKER is the vice president of new market initiatives at the JR Simplot Company, a \$4.5 billion private corporation with fertilizer, food and livestock divisions. At Simplot, he works on identifying and commercializing new technologies and opportunities across the agricultural space. He is the general manager of Simplot's plant-sciences business.

Dr. Baker has significant experience in the biotechnology industry, including working with several start-ups and managing a proteomics research lab at the Barnett Institute in Boston. Prior to joining Simplot, he also worked as an investment professional at Clarium, a global-macro hedge-fund company in New York.

Baker has a BS from Yale, a PhD in chemistry from Northeastern University, and an MBA from Harvard Business School. At Harvard, he worked with Clayton Christianson on concepts developed for the Social Innovation Fund.

Technology Evolution in Vegetables

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Biotechnology has played an important role in driving new products for agriculture, and has changed the way growers think about controlling insects, for example As head of our field organization, I spend a lot of time with growers and see firsthand the advantages of modern technologies, and, as a scientist, I get of a lot of satisfaction out of that. We should think of this infusion of biology—driving agricultural innovation over the last 25, 30, 40 years—in a much broader sense.

INNOVATIVE TECHNOLOGIES FOR AGRICULTURE

Transgenic technology was the first generation in using modern biology to improve agriculture and bring novel products to the marketplace. This has also driven innovation in terms of how we think about breeding, and how we think about trait associations, and delivery of new traits to the marketplace, whether it be through transgenics or through advanced breeding technologies. It's now playing out, for us and for other players, in a new sector that we call "Ag Biologicals" (Figure 1). The more we understand about basic biological processes—the more we understand at the genetic level—we can begin to think in terms of transforming the biological sector with very innovative technologies.

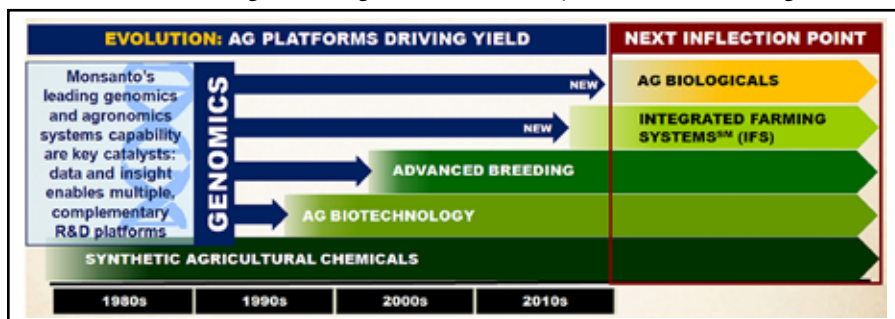


Figure 1. Bringing genomics to the field with integrated farming systems and agricultural biologicals.

We think about genomics in terms of the ability to understand, at a genetic level, how traits play out. It's a key piece of advanced breeding methodology and we see it also as a key piece in understanding how to drive value in the Ag Biologicals sector.

I had the pleasure of heading Monsanto's insect-control program in the 1990s, when we were developing YieldGard® and Bollgard® and did the first work on corn rootworm. Seeing the impact that these technologies have had at the grower level has been tremendously satisfying, particularly in terms of reductions in insecticide-spraying (Figure 2). Growers were applying insecticides to sweet corn up to 20 times in a season. In the southeast some had to spray daily or even twice a day in order to prevent visible damage.

SWEET CORN

For sweet corn, the acceptable level of insect control is the absence of worms when the ear is opened. There is very little tolerance for damage to the ear, which is why heavy spray regimes were necessary. Tony Shelton's data¹ backs this up as well. Clearly, this situation is tailor-made for *Bt* technology (Figure 2). The reduced damage that the retail sector is looking for is achievable. It's a tremendous advantage with transgenic technology. On the other hand, the advantage is difficult to talk about at a consumer level because most people don't think about how often sweet-corn crops are sprayed before they reach the marketplace.

There's been a lot of discussion at this conference on the regulatory system and costs of achieving deregulation. One advantage of this transgenic technology is that the event we

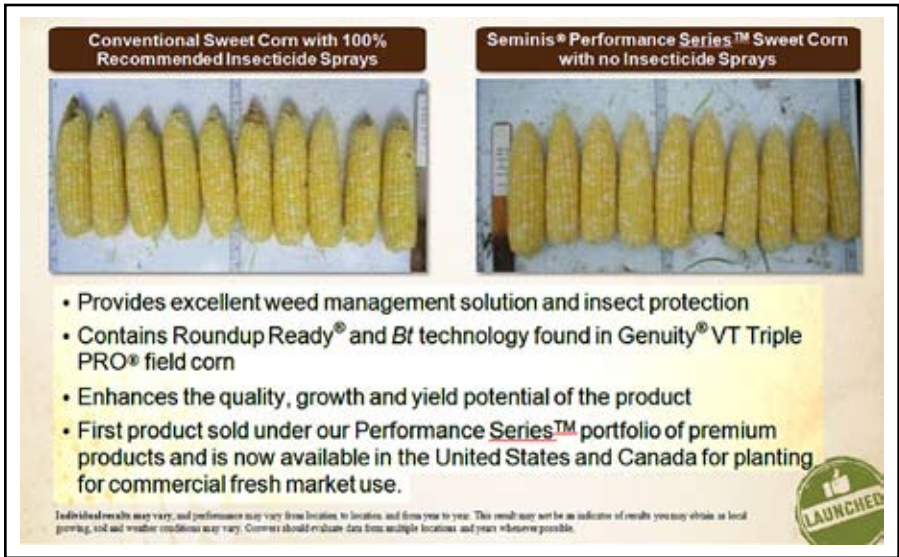


Figure 2. Biotechnology: Seminis® Performance Series™ sweet corn provides protection against insect predation.

¹Pages 49–58.

used in sweet corn was the same as that in field corn. When the event has been previously approved, fewer steps lie ahead in the deregulation process. This helped us to justify the cost of deregulation in terms of the market size we were going into. This has been launched in the United States at the grower level. Some challenges occurred at the retail level, but it is now actually working pretty well for us. The overall benefits of this technology make it very advantageous. The other product we have in the marketplace—created using a transgenic technology—is virus-resistant squash. It’s been available for a number of years. Again, it has grower advantages from a productivity standpoint.

ADVANCED BREEDING TECHNIQUES

Our major play in vegetables is to take advantage of advanced breeding techniques, which entail the ability to associate, at the genetic level, from a trait perspective back to a molecular marker which allows our breeders to be more efficient in making selections (Figure 3).

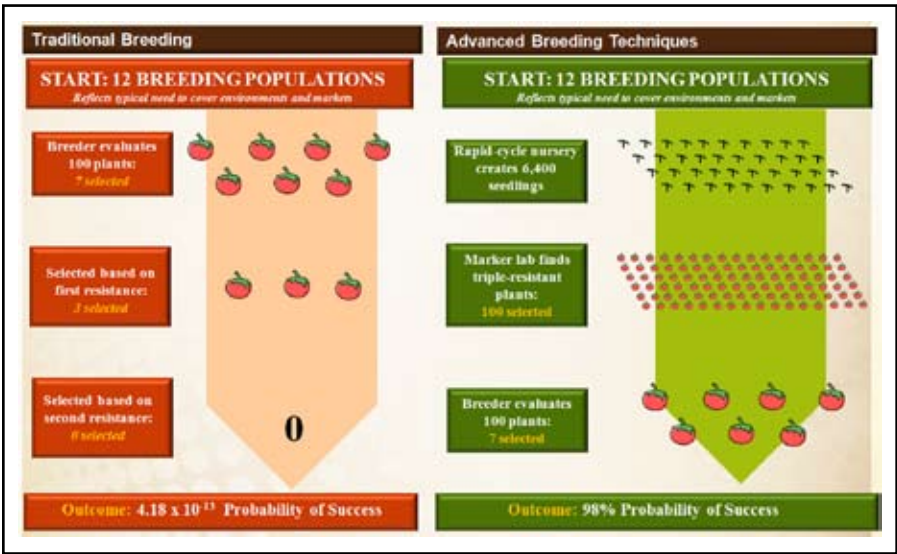


Figure 3. Advanced breeding: Faster product development tools, capability and capacity enable successful delivery as never before.

In many cases, known molecular markers are for disease resistance. With those markers “built in,” breeders can focus their efforts on aspects of quality—size, shape, color, taste—that have appeal in the marketplace. With respect to new advanced technologies, momentum is driven by the ability to identify and fine map markers and introgress them rapidly (Figure 4). Seed chipping² is proving to be a major driver as it simplifies breeding.

²Designed by our engineering colleagues at Monsanto, chipping allows us to determine the genetics of a seed without destroying it.

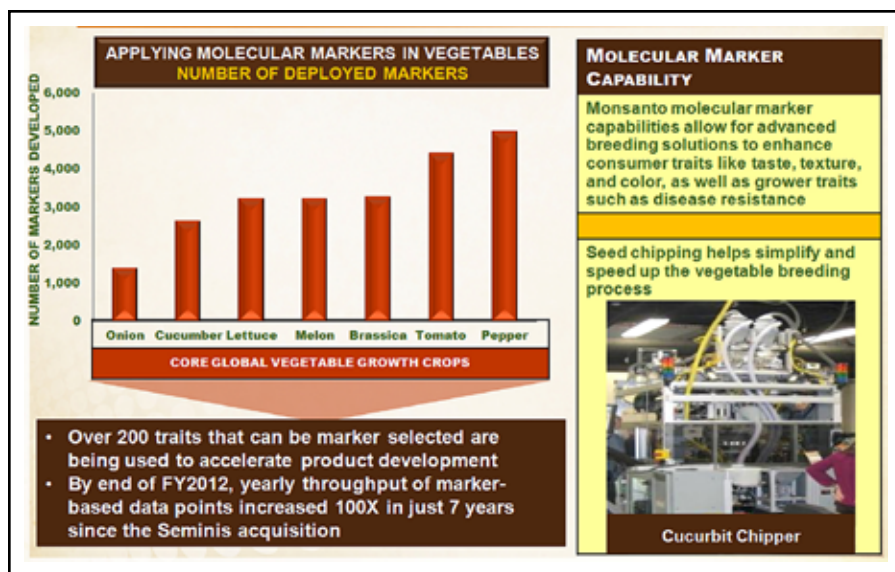


Figure 4. In vegetables, advanced breeding capability accelerates new product development and growth opportunities.

We have identified thousands of markers in vegetable crops (Figure 4). Yearly throughput of marker-based data points has increased 100-fold since our acquisition of Seminis in 2005. Similar acceleration is occurring across the industry, not just within Monsanto.

PHYTOPHTHORA IN PEPPER

Of course, it does little good to have a lot of whiz-bang technology if it fails to provide value to growers. *Phytophthora* is a major disease of peppers globally, and we have applied marker-assisted breeding to improve resistance. The source of resistance can be incorporated into other pepper types (Figure 5).

Once the donor source of resistance is identified, the marker for the trait can be identified and introgressed into any number of plant types: jalapeños in Mexico, blocky peppers in the United States, chili peppers in India, *etc.* Field evaluations visually demonstrate significant improvements in resistance of manipulated peppers to *Phytophthora* (Figure 5). However, this is only part of the story. It is essential that the disease-resistant pepper retains the characteristics—heat level, taste, color, shape and size—that growers and consumers expect.

DOWNY MILDEW IN CUCUMBER

Another example is resistance to downy mildew, a major disease of cucumbers. By introgression, we have conferred resistance and commercialized American slicer cucumber varieties in the United States (Figure 6). With the same technology, we will commercialize Beit Alpha cucumbers for the Middle East market, even though these are totally different kinds of cucumbers.

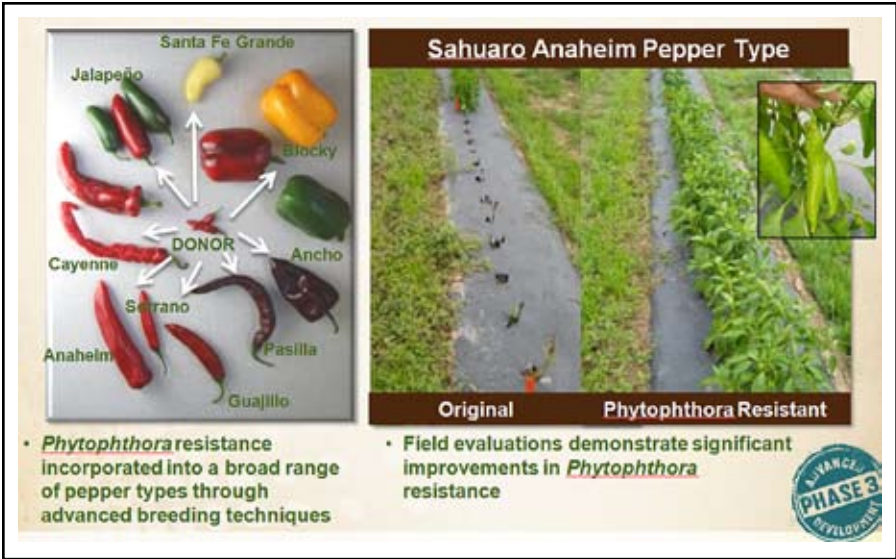


Figure 5. Broadly applying marker-assisted breeding to improve resistance to *Phytophthora* in peppers.

The benefits of technologies that provide fungal resistance are analogous to those that provide insect resistance, Bollgard® and Yieldgard®, in terms of conserving yields and lowering input costs, in this case by reducing need for fungicide applications. Also, there is a systems advantage in achieving less damage from disease by exploiting the plant's genetics.

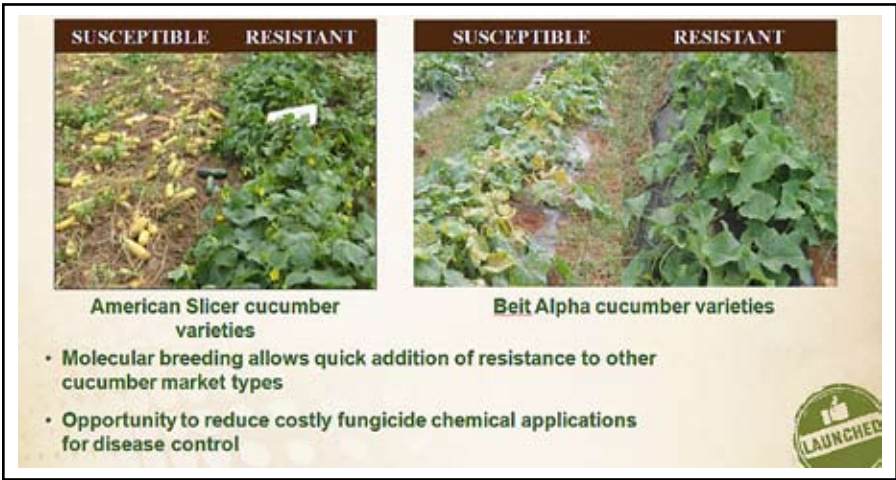


Figure 6. Resistance to downy mildew would improve grower returns in multiple varieties of slicing cucumbers.

BioDIRECT

Ag Biologicals are being more widely used in vegetable crops than in the large-acreage row crops, corn, soybean and cotton. They are particularly advantageous when used in protected culture, *i.e.* within net houses, plastic houses, or glass houses, in which finer environmental control is possible, allowing the biologicals to be used more effectively.

DNA-sequence-based information is available to identify pest targets and to provide active agents that knock out those targets. The pest may be a weed, insect or a pathogen—a virus or a fungus—and the ag biological shuts down a key pathway and controls the pest or pathogen (Figure 7). We heard from Neal Carter and Haven Baker about gene silencing and, basically, what it entails. This approach is in the early stages of development, and a lot of work is aimed in this direction globally.

Figure 8 shows examples with lab trials with pepper and tomato; non-transgenic BioDirect technology clearly provides protection in plants infected with viruses.

We believe that this approach will fuel a resurgence in the use of biologicals and drive the ability to make them even more beneficial than they are already. And we're not alone. Several major agricultural companies are investing in this sector; clearly, it's something that people are excited about. The more we understand at the molecular level, the more we can target specific processes to shut down—to control pathogens and pests—the more advantages we will extract from biological control methods and the more products will be launched in that sector.

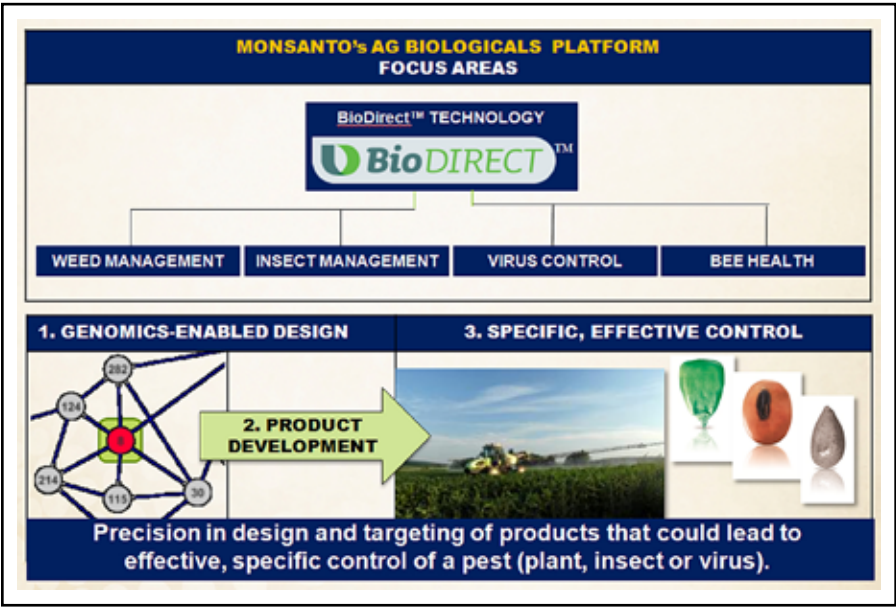


Figure 7. Ag biological: A new class of agricultural biological with the potential to deliver effective crop protection.

I want to stress that as we think about biotechnology in vegetables, there remains a role for “classic” transgenic technologies. And we, and other companies, have some such products in the marketplace. But we also are thinking about this more broadly. The next iteration will be BioDirect and other mechanisms. We are early in the developmental process, but feel that it will help us make strides in the vegetable sector.

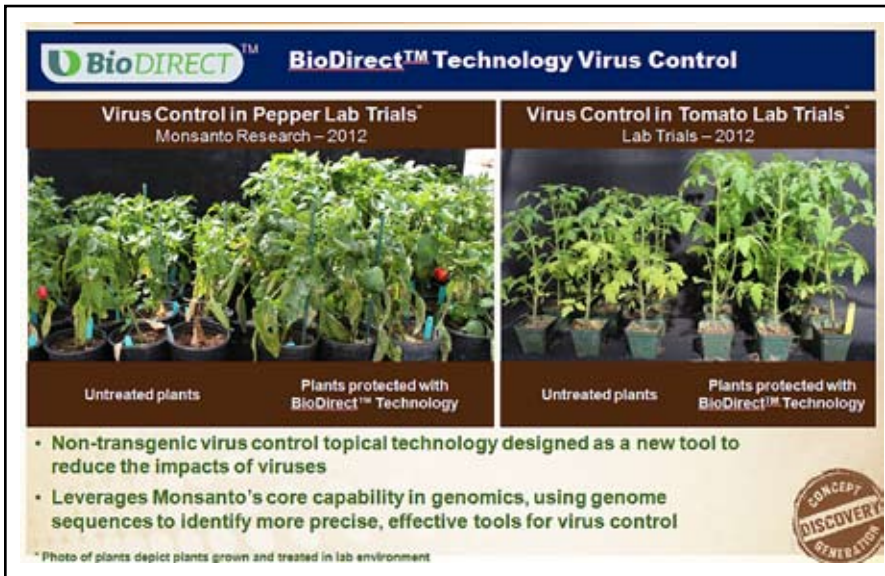


Figure 8. Initial testing indicates that BioDIRECT™ technology could reduce virus-disease symptoms.

Certain statements contained in this presentation are “**forward-looking statements**,” such as statements concerning the company’s anticipated financial results, current and future product performance, regulatory approvals, business and financial plans and other non-historical facts. These statements are based on current expectations and currently available information. However, since these statements are based on factors that involve risks and uncertainties, the company’s actual performance and results may differ materially from those described or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, among others: continued competition in seeds, traits and agricultural chemicals; the company’s exposure to various contingencies, including those related to intellectual property protection, regulatory compliance and the speed with which approvals are received, and public acceptance of biotechnology products; the success of the company’s research and development activities; the outcomes of major lawsuits and the previously announced SEC investigation; developments related to foreign currencies and economies; successful operation of recent acquisitions; fluctuations in commodity prices; compliance with regulations affecting our manufacturing; the accuracy of the company’s estimates related to distribution inventory levels; the company’s ability to fund its short-term financing needs and to obtain payment for the products that it sells; the effect of weather conditions, natural disasters and accidents on the agriculture business or the company’s

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Herbicide Information for Performance Series™ sweet corn: Make sure the intended use is approved in your state. Do not use this information as the basis for any glyphosate product other than Roundup® branded agricultural herbicides. You must have the supplemental labeling for use on Performance Series™ sweet corn containing Roundup Ready® technology and the product label with you when making the application.

Performance Series™ sweet corn Insect Resistance Management (IRM) – Post-Harvest Requirements: Crop destruction must occur no later than 30 days following harvest, but preferably within 14 days. The allowed crop destruction methods are: rotary mowing, discing, or plowing down. Crop destruction methods should destroy any surviving resistant insects.

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JOHN PURCELL is vice president for technology development for Monsanto Vegetables and serves on Monsanto's vegetable leadership team. In this role, he heads a global effort responsible for supporting the commercialization of vegetable seed products in diverse markets. He is also a senior technology

fellow at Monsanto.

Previously, he served on Monsanto's technology leadership team, in which capacity he oversaw a portfolio of technologies and products in the pipeline that bring increasing value to the cotton industry globally. Prior to that role, he held numerous positions in Monsanto's technology organization. He headed a research site in Mystic, Connecticut, and led a research program in Cambridge, UK, focusing on corn and wheat, respectively. Dr. Purcell spent more than 10 years at Monsanto's biotechnology R&D center in St. Louis, where he held jobs of increasing responsibility in the biotechnology research organization. For several years, he headed Monsanto's insect-control program. His role was later expanded to include all plant-protection research including insect, fungal and nematode pests.

Prior to joining Monsanto, he was a postdoctoral researcher at the US Department of Agriculture. His PhD was granted from the University of Massachusetts at Amherst in molecular and cellular biology with an emphasis on insect biochemistry. He is an inventor on several patents and an author of numerous scientific papers, reviews and book chapters.

Case Studies

Q&A

MODERATOR: DANIEL LINEBERGER

*Texas A&M University
College Station, Texas*

Alan Bennett (University of California, Davis): This question is for Ricke Kress on citrus greening. I recall in the National Academy report some discussion of delivering a resistance trait through rootstocks. Is that being explored in terms of delivery through a transgenic rootstock, for citrus or other woody species?

Ricke Kress: Yes. It is part of the industry-research effort. It's a determination to elucidate the relative importance of the scion or the rootstock or both.

Chris Wozniak (US Environmental Protection Agency): I have a question regarding some of the surveys a couple of you mentioned relative to people's perception of putting DNA back into the same species and whether you want to call it intragenics or cisgenics or Innate technology or whatever. Do you think that the people answering those questions really understand the difference as to whether you are plopping in an ORF or a new promoter? Do they really understand differences in, say, the amount of the trait that will be expressed in your version of the plant versus where you are getting the gene from?

Haven Baker: The answer is no.

Wozniak: That's pretty much what I figured.

Carter: We didn't try to differentiate between transgenic, cisgenic and intergenic.

Wozniak: I'm curious because in years of talking with people who are in this research—and reviewing grant proposals—everybody seems to tout their own version of what is cisgenic and what is intergenic and why theirs is better than the last guy's. One of the things that we have considered is that if you do manipulate control elements, promoter sequences, then you are dealing with a different scenario because then you are changing the tissue and expression pattern of that trait protein or whatever it is, as compared to, say, eating the same thing you have always been eating because the gene came from potato and it's in potato. Whereas when you do those manipulations it's not really the same, at least to some ways of thinking.

Baker: Scientific distinctions are usually lost on the general population. It's confusing if you use Google alerts of the reports of what you think the public perception is. Data generated by the International Food and Information Council is reasonably neutral—I hope—when they ask people, “Do you support biotech in your food?” They get answers similar to ours. Then you ask the next question, “Do you know if biotechnology is in your food?” and two thirds of Americans say they don't know and another 10% say no. So you are asking for opinions on subjects that consumers are largely uninformed of and probably want to stay that way as long as it's safe. So, yes, these distinctions get lost on the majority of the population, but 8% of people—it correlates highly with the organic crowd—are very against technology and very vocal. That's generally who we think about and who we hear about. It's a hard thing to get your arms around what people really think.

Audience Member: My question is again related to cisgenic and intragenic versus transgenic. When you are dealing with USDA-APHIS, FDA and so on, does that make your life easier?

Neal Carter: We never made the distinction. We just call it transgenic. The regulatory process essentially is the assessment of risk and the data package addresses that. If you can build a vector that is simpler, or do something that is going to require less data, than the regulatory process will be easier. But, at the end of the day, you have to address the risks.

Haven Baker: One more thing on why we did what we did. In the case of potatoes—and also tomatoes—you've already had market failures. Growers have long memories and so do industry participants. We talk about the Innate™ technology, partly to differentiate it from past efforts. That's not really geared toward the regulatory aspect. It's geared towards consumers, and, in our case, towards industry.

Roger Beachy (Global Institute for Food Security, Saskatoon): Two questions. We heard from oranges about \$3.2 to \$3.4 million for all the tests for regulatory approval of a new protein entry, and I didn't hear that in apples. I wonder if you would comment on the differences there and what does that reflect? Then I want John Purcell to address the issue of would you have done *Bt* sweet corn if you had to go through the whole process of deregulating the event rather than crossing it in?

Carter: From our perspective it's hard to define regulatory costs. I'm not sure what is meant by that. A lot of the costs—such as for field trials—you will incur anyway. I think I heard Dennis say a quarter of a million dollars—that kind of range—nothing like three or four or five million. But we haven't finished yet. Maybe we are going to see more costs.

Kress: We have looked at what we feel we have to do to work our way through the process identifying all the potential tests and data collection and so on that we have to put into our package. We are going to do what we have to do. I also have a board of directors that is very interested in what we are doing as well, so I need to give them some insight as to how this can work.

Carter: There's an important distinction, in that we are not going through the EPA. Also I'm not including the cost of the field trials and the 10 years of field data that we generated that we wanted to have ourselves. I'm thinking more of the incremental cost of putting those data together and doing the statistics on it in a way, shape and form that the regulatory people wanted to see it done. Maybe there's a few additional studies that we did, and then the sequencing of the events themselves. We hadn't fully sequenced them, we relied on Southern data and we went ahead and sequenced them—just some extra things we did for regulatory purposes.

Kress: In the scheme of economics, the regulatory package might be the cheapest part. When we start to build these trees and to commercialize them and move into the growth side of it, it's going to be expensive because with the new regulations on nursery operations, and so on, for every 100,000 trees in citrus right now it's about a million dollars to build a structure to meet all the requirements and handle it all. There are 60 million trees in the state of Florida, so there's a lot more to the puzzle.

Daniel Lineberger: There is a follow up question for John about sweet corn.

John Purcell: Let me provide a little context first. At Monsanto, as a scientist, you feel fortunate because there are significant investments in R&D, but there is also a stringent process for every project, and one of the milestones it hits is when it goes into the regulatory phase, because that's when you start assuming the regulatory costs. In each stage of the discovery process, we make priority decisions on which projects move forward. The challenge is in a lot of the vegetables. If you look at the number of markets in which we have to go for cultivation approvals alone. Look at tomatoes: It's a big market opportunity, but it's not like corn, cotton and soybean. It's a very distributive kind of market. It's \$500,000 to \$1 million at a time. So, when you look at those kinds of markets it's difficult to say whether you go a product-development route that will require the regulatory piece. Looking at that many cultivation approvals and then the import approvals for where those products are flowing, the numbers don't pencil out. Part of the stringency is what's called APV: at present value. When you look at the cost of developing the product and what will be the eventual return, and then the other piece that is in there is the risk

adjustment on that, which is what is the chance of getting all those approvals in order to have that commercialization. So a lot of these vegetable products from the transgenics just don't pencil out. The corn one—that's an interesting question. We started with the approval and so it wasn't a hard decision for us. I haven't done the numbers but I'd be skeptical. When you pencil it out could you justify it with the US market and then you look where else that corn would have to be produced if you didn't start with mon88 and mon89 which are already approved?

Peter Schuerman (Texas A&M Agrilife Research, College Station): The Arctic apple story is fascinating and it's particularly interesting that such a small company would take on that task. Your future plans include some protein traits. How will you finance those enterprises in the future?

Carter: We have to do this with Arctic to prove that we *can* do it. We have a grower group that I am part of that has always known that there is a lot of money in something that is new and different. With a GM apple, we aren't sure if that's still going to be the case because of the consumer push back. We have learned a lot regarding how to do it faster. We've learned how to negotiate the regulatory process. The science is actually relatively straightforward, and the great thing about it is that it works. We will chase the money, I guess, and apply for grants and leverage, we've been able to leverage our shareholder capital about 4 to 1 from a research point of view. It's very easy to fund the research. You don't get any leverage on the precommercialization component, which is the shark pit—the chasm you have to walk through that is very, very difficult. Dennis called it the Red Zone. The Red Zone for him included the regulatory piece. For us it's more the precommercialization phase, understanding the industry that you are working in, having an intimate idea of whom to talk with and how to sell it and maybe how to get a few key big companies involved to help steer that process. In fact, in all of the new traits we are working on, we have large tree-fruit-growing companies, usually vertically integrated, that are interested in that product and they will help partner in that cost.

Lineberger: So, they are investors?

Carter: They're not shareholders. It's fee-for-services-type work.

Schuerman: Venture capitalists?

Carter: Yes. These are people who got in early before they read the fine print: "Neal, what did you talk me into?" My wife and I are the two largest shareholders and so I guess we are just stupid or something. We have about 40 shareholders and half of them are fruit growers—people who are willing to speculate on being part of something new. I'm lucky. I'm involved in some other business activities and I dragged some of those guys in too, and maybe they aren't feeling so lucky, but I'm feeling lucky.

Purcell: With the portfolio process, it's rarely the technical feasibility that kicks things out on the vegetable side—insect control, virus control, those kinds of things we know we can do. Being with growers pretty much every day the value in there is there but when you think about how all the elements in the chain have to come together to do that, and then the international elements as I discussed, that's where it gets really problematic.

Tony Shelton (Cornell University, Ithaca): We've all heard about how great this technology is, but the main issue seems to be communication with the consumer. And I see, Neal, that you have a nice little friendly label, and people can go to your website and learn more about it. What happens if, all of a sudden, you have to slap a label on there that says "genetic engineered" and you don't not have control over the friendliness of the message. How will you deal with that?

Carter: If mandatory labeling laws come in with a skull and crossbones or something, sure it's not going to help. But identifying Arctics as Arctics with point-of-sale literature available—and these kinds of things—I don't think it will change much. I think that there is going to be fairly widespread understanding that this is a genetically engineered apple.

Shelton: And Rick, what about that for citrus? It's not going to apply to the fresh market, it's more for the juice.

Kress: No, it will be fresh as well. Although we are in Florida this is going to be a process that is going to have to go through the entire regulatory approval for the United States. It will affect all of citrus in all directions. From our perspective, we recognize the work that we are going to have, education-wise. With the various research that we have going, we are kind of in a horse race. We have several horses that have broken from the gate and as we go towards the third pole we will start to narrow that down and when we start looking towards the fourth, the finish line, that's when we will step out and become more involved in that overall education process because we will know the direction we are going. We can't work on an education process today with three different directions. That won't work. When we get to the direction we are going in and then we will move forward on education before we get commercial.

Christiane Deslauriers (Agriculture and Agrifood Canada, Ottawa): The objection that I hear most of the time from industry is the unpredictability of the regulatory system. The biggest impediment to progress in this kind of work is not knowing what the regulatory system is going to be. Given your experience, do you think it is realistic to ever think you will be able to know ahead of time—the question will be knowable ahead of time? And to what extent has that applied for each of you?

Kress: Part of our challenge has been that we are working with a tree. We are not working with a corn plant, potato or other annual. There is a gap in the information that the agencies have. The first time we went to DC and met with the agencies, we went with the

intent of asking a lot of questions and we were very open with what we were doing. So, we are working very closely with all three. I judge the quality of the meeting that we have when we are in DC by the number of questions that I come home with, and generally I come home with more questions than answers. That's okay, because that's what we have to do to get through this. That's how we are looking at it. We wish there were a template, but there isn't. We are going through step by step, and trying to be proactive.

Purcell: Roger Beachy talked about the inconsistency on the world stage and that's where we, a global seed company, see much unpredictability. Think about emerging and growth markets in Asia market where they might not even have a regulatory system in place. So you are developing your product while the regulatory system is being constructed and that's where a lot of the uncertainty comes in because you don't have harmonization. In many cases the rules are being written as people are trying to develop products and that, obviously, introduces a lot of uncertainty in when you can expect an approval or even what you have to do to put a submission together.

Carter: The smaller the company the bigger the uncertainty in terms of risk caused by regulatory timelines. You have a burn rate, but you don't know if it's going to take two years, three years, four years or five years. It's hard to know when you are going to get into the marketplace and start to see return on investments. In January 2012, we met with APHIS and FDA and a timeline was given. But, you leave the meeting and immediately there is slippage, and then they come out with their new timeline process and immediately there is more slippage. Such uncertainty builds risk and, typically, boards of directors and shareholders don't like risk. If you are trying to raise money they are going to say, "Yes, but what about the regulatory thing, where are you with that?" And you say, "Well I don't really know. We thought we would be done but we're not." These things are definitely impediments to raising capital.

Tom Redick (Global Environmental Ethics Counsel, Clayton): We've seen the labeling laws in Europe cost us literally billions in trade, measured by European economists who are very objective. The Connecticut labeling law has to include at least four states contiguous states. Assuming a bunch of states in the northeast enact a GM-labeling law, would that significantly impact your ability to go forward with your orange or apple or potato?

Kress: It's not going to slow us down because if we don't find a solution to this disease we're not going to have citrus. That's the bottom line there. Another thing, which, in a backhanded way, is in our favor, we won't be introducing tomorrow. We've got some years yet, still involved in this, so we are anticipating that this is all going to get sorted out. Again, a lot of companies that market orange juice are interested in how this will play out. On one hand we have time, and on the other hand we don't. It's all got to work.

Juan Landivar (Texas Agrilife Research, College Station): I think you said that you have until 2019 for deregulation. Where are we going to get our orange juice? From Brazil?

What is the plan? What is going to happen? Is there any way that the process can be accelerated?

Kress: I didn't go into all of our research. We have some other approaches that could provide interim solutions to shorten that timeline. One has to be optimistic. My board of directors asked me one time how we were addressing all of this and I said that I'm optimistic six out of seven days. They said, "What day aren't you?" And I said, "Well, that's the problem, I never know which day it's going to be."

Tom Turpen (Citrus Research and Development Foundation, Lake Alfred): For Neal—I thought it was brilliant—the selection of the trait and how it benefits the participants along the whole value chain. And also the communication of the technology—it was the best description of RNAi I've ever seen, with the railroad tracks. I wonder if you could preview for us the story you will use for the infectious-disease traits, because those will be adding a PIP. You did such a good job of communicating your Arctic apple story, how will you communicate your infectious-disease traits?

Carter: I don't quite have that story mapped out yet, so I can't answer your question, sorry. It would be premature at this stage. But, a couple of things—we go to see US Apple in Washington and they say, "Oh, if you had an agronomic trait, we would really like it because our growers would be behind it." And we respond, "Yeah, but consumers are the ones you have to please." So, we are really frustrated by the fact that every industry group we meet with—growers, grower/packers, shippers, their industry representative groups—they all want agronomic traits, and they are willing to support those and stand behind them and promote them and all the rest, so maybe we won't need to. We chose our trait because we felt that we needed to get the consumer on our side and that if we just jumped into scab or fire blight right off the start, we would be dead in the water. So they will be Arctic plus. They will be non-browning with fire blight resistance, non-browning with storage scald resistance—that sort of thing.

Lineberger: Just to put a little plug in here for Neal—if you go to his website there is a link to his TED talk on the integration of biotechnology. It's fascinating. He uses some very common-sense non-technical easy-to-understand approaches.

Session 3-1: The Regulatory Process and Technology Access for Specialty Crops

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Regulation of Plant-Incorporated Protectants by the US Environmental Protection Agency

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A plant-incorporated protectant (PIP) is a pesticidal substance produced by a gene that has been inserted into a plant through transgenesis. EPA does not regulate the plant; in contrast to other regulatory agencies, we regulate the gene and the gene product.

As pointed out by Roger Beachy¹, the definition of a pesticide has been around since 1947, when the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) was promulgated. In addition to language about destroying, repelling, and/or mitigating pests—“pests” are defined in the statute—it deals with plant regulators (not plant-growth regulators). Admittedly the category is broad, but then “pesticide” is difficult to define.

As far as I know, there is no inclination or intention to regulate plants expressing plant-growth regulators as pesticides, although, certainly, a policy statement to that effect might be helpful. Today, I am speaking specifically about plants that are disease- and/or pest-resistant.

Four statutes influence our authority to regulate PIPs (Figure 1) of which I will focus on FIFRA, the main pesticide law, and the Federal Food Drug and Cosmetic Act (FFDCA) that we share with our colleagues at the Food and Drug Administration (FDA) regarding residues and tolerances.

FIFRA is unusual in terms of environmental statutes in that it considers benefits as well as risks, which is crucial with compounds that are inherently more toxic—typical nematicides, insecticides, *etc.*, for example—but it can apply to PIPs in terms of environmental safety or benefits and even economic safety and benefits. This does not apply to the Food Drug and Cosmetic Act.

¹Pages 19–28.

- **Federal Insecticide, Fungicide and Rodenticide Act – (FIFRA) pesticides**
- **Federal Food Drug and Cosmetic Act – (FFDCA) food and feed safety**
- **Food Quality Protection Act - (FQPA) amends FIFRA and FFDCA; sensitive groups included in assessment**
- **Endangered Species Act - (ESA) any impact on threatened or endangered species**

Figure 1. EPA's regulatory role.

In terms of initiating the process of achieving deregulation, most typically applicants start with an experimental use permit (Figure 2) to generate field data. It is particularly noteworthy that we do not generally regulate field trials at less than ten acres. Trials in excess of 10 acres are likely to be under an APHIS permit or notification process. If you're clever about it, you can plant multiple 9-acre plots, depending on how you design them. It is about cumulative acreage, but addressing a specific question with each cumulative 9.9 acres is acceptable and is not regulated by EPA as long as different pest-crop combinations are being evaluated in the plots of less than 10 acres. The point is to assist in the development of data characterizing the product and/or its chemistry that will be needed to ultimately achieve registration; it is not about producing seed for commercial purposes and the data generated cannot be used for promotional purposes. Of course, we need to know the origin of the transgene, its DNA sequence and the deduced amino acid sequence. Where *Agrobacterium* has been used, a plasmid map will be necessary. Also protein-expression levels are needed, typically determined at multiple stages in the plant's growth as well as at multiple locations; this need results from oversight being defined through a law governing pesticides. The content of the pesticidal substance must be elucidated, which is true for all pesticides, whether it's a liquid, a PIP, or a microbial compound. In addition, for purposes of insect-resistance management, it's important to know the accumulation of the protein in a leaf at whatever stage. That's particularly true with corn and cotton, and then, of course, an analytical method is required to detect the pesticidal substance, which is particularly important in trade.

Each event has a unique OECD² identifier. Although we often look at things parochially, we must keep in mind that we are in a global economy. From a scientific standpoint, I understand why people often say, "We are familiar with *Bt* and it would be nice to just give it a pass from now on." On the other hand, the Chinese, Koreans, Japanese, Australians, Brazilians and others may not agree with that. Putting a new product on the market

²Organization for Economic Co-operation and Development.

- **Cumulative acreage ≥ 10 A (4 HA) terrestrial or ≥ 1 A aquatic per year per pest requires EPA approval**
- **Food / feed tolerance required (at any size)**
- **EUPs are all time limited and require reporting of results as well as any adverse events**
 - [6(a)2 of FIFRA]
- **Products of EUPs are not eligible for advertising or promotion, but can be marketed with a tolerance**
- **EUPs are for research purposes**

Figure 2. Experimental use permits.

needs to be done with some forethought prior to actual commercialization. Asynchrony in approval is an ongoing problem in international trade.

For the vast majority of our guideline studies, test substances are proteins, which are often generated in a yeast or *E. coli*-based fermentation system (Figure 3). It is then the responsibility of the applicant to demonstrate the equivalency of the protein produced in the model system to that produced in the plant. To assess human-health effects of PIPs, we run acute oral toxicity maximum hazard dose tests with animals. Admittedly unrealistic, they are run for short periods to show any potential toxicity. In some other countries, long-term feeding studies are the norm, to reveal chronic and sub chronic toxicity. We have this option available if the first-tier testing indicates that there might be an issue.

- **Proteinaceous test substances are often produced in microbial systems**
- **It is the responsibility of the registrant to ensure the test substance from the native source (*in planta*) and microbe are equivalent**
- **Mr, MALDI-TOF / MS, and glycosylation status are all parameters to examine**
- **Bioassays can also be informational in establishing equivalency**

Figure 3. Test substances.

Biochemical properties are assessed. If the protein is an enzyme or a toxin that binds something, that needs to be demonstrated. Importantly, we do a lot of hematology comparisons both for toxicity and for allergenicity, based on known toxins and known allergens. In addition, digestibility studies assess allergenicity as well. This raises another point: when choosing a gene for transgenic work, it's best not to use a shellfish or a tree nut as the source, as it will raise red flags. That's not necessarily an insurmountable issue, but it may be costly in time and money.

In terms of the environmental or eco-assessment, non-target effects are a chief concern, on vertebrates and invertebrates alike (Figure 4). Because we are dealing with pesticides, environmental fate is also an important issue. What happens to the pesticidal substance: does it bind to clay particles, does it dissipate or is it degraded? In addition, does the transgene in question move outside of the cropping system to an indigenous or even feral relative? If so, it is something that we would consider in terms of potential adverse effects on the environment. If a tolerance is in place—in other words if we approve the gene product for consumption in animal feed or human food—then crop-to-crop gene flow is not an issue for us, although it may be an issue for USDA-APHIS. We require that, once you get to the field-trial stage, tolerances should be in place.

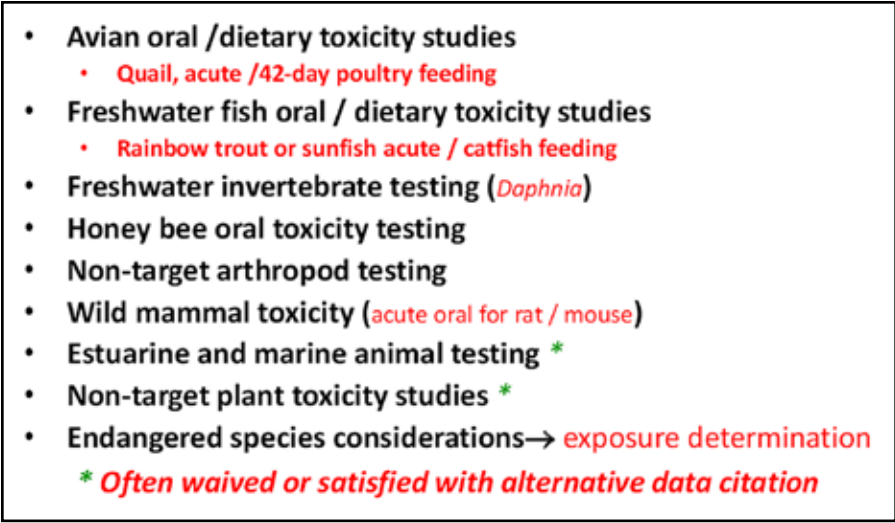
- 
- **Avian oral /dietary toxicity studies**
 - **Quail, acute /42-day poultry feeding**
 - **Freshwater fish oral / dietary toxicity studies**
 - **Rainbow trout or sunfish acute / catfish feeding**
 - **Freshwater invertebrate testing (*Daphnia*)**
 - **Honey bee oral toxicity testing**
 - **Non-target arthropod testing**
 - **Wild mammal toxicity (acute oral for rat / mouse)**
 - **Estuarine and marine animal testing ***
 - **Non-target plant toxicity studies ***
 - **Endangered species considerations→ exposure determination**
 - * Often waived or satisfied with alternative data citation**

Figure 4. Data required for ecological effects on non-target organisms.

Figure 4 also shows some instances where corners may be rounded off to save some money. Some are very likely to be applicable—avian oral toxicity for a protein, for example. Typically, the mammal test has already been done; for human food tolerance, that study suffices. Although all of these data requirements need to be fulfilled, not all of them need to be fulfilled with empirical data generation; some may be fulfilled with a waiver rationale. My attorneys warn me not to call it a “waiver” because that has specific legal connotations. But it’s a rationale. It may be a couple of paragraphs, a paper from

the literature, or it may be based on an exposure argument showing that the PIP will not affect a target organism or other source of concern. There are ways to get around that. We have never had a PIP produced in a marine or estuarine environment, so we've never asked for a grass-shrimp test.

We don't put a lot of weight in the 42-day poultry-feeding study, although other countries require it. Many of our registrants submit that, in which case we review it, but good data are needed from several other tests prior to getting to that stage.

NAVIGATING EPA

EPA sets tolerances—maximum residue levels—for pesticides in or on food and feed products. A pesticide residue present in or on a food or feed product that is not covered by a tolerance, or an exemption from the requirement of a tolerance, means that the product is considered “adulterated” under the FFDCA and the FDA is responsible for enforcement. That is to be avoided.

Tolerances are set by considering data from acute oral toxicity tests, sequence comparisons to known toxins and allergens, *in vitro* digestibility and the source of the gene. We look at homology to known allergens; a good database is available at the University of Nebraska. It's important to do such searches prior to progressing significantly, *e.g.* when building the constructs to verify that, by chance, the protein of interest doesn't have a hit, *i.e.* a 35% or greater homology over an 80 amino acid stretch. If that is triggered then more testing will be called for.

Frequently, people call and take advantage of our guidance. It's best to do so early on and not while in the midst of field trials only then to discover a problem.

As mentioned, most data requirements are designed for proteins as the test substance. If an RNA-interference approach is possible, it is likely to save time and money. People are spraying double-stranded RNAs, and bacterial vectors are being used to move RNAs into the environment. Although they're not proteins, questions remain in terms of how bioinformatics may aid predictability of action toward non-target organisms. For example, do the RNAs quickly degrade after contact with the soil? A number of questions need data generation. Clearly, RNAi won't solve everything, but where its use is possible, it should be considered. In addition, when inclusion of inert ingredients is needed, *e.g.* antibiotic and herbicide-tolerance markers, it makes sense to choose those that have been previously approved—glucuronidase, NPTII, EPSPS, PAD, *etc.*—again to save time and money.

Approval of green fluorescent protein has not yet been requested. The first such request will incur the cost of the required assessment. People have told me that a viable alternative approach will be to fuse NPTII and GUS. On the other hand, the tolerance for each of those individually may not apply to the fusion protein because truncation will change the sequence. Little things like that can cost more time and more money and, again, it's wise to contact us early—which doesn't cost anything—and hopefully, we can be of some help.

Now, in terms of the “barriers” that EPA's Office of Pesticide Programs promotes, PRN 11-3 (Figure 5) denotes the third notice issued in 2011 that provided guidance—in strong terms—for provision of data for applying for pesticide registration under FIFRA section 3

and FFDCA sections 408 and 409. The agency has a history of requiring particular formatting, to which there are advantages. In terms of record keeping, it lends efficiency when things are put together similarly and we have to find a piece of information pertaining to one of the thousands of products that we register. Initially it can be intimidating. We produce a registration manual that provides basic information (Figure 6). However, if you've never been through the process before, it can be helpful to employ an experienced consultant for guidance. We can provide a list of those who have worked with us, but we don't recommend specific people. On the other hand, some people have gone through the process without a regulatory consultant. Ralph Scorza and colleagues at USDA-ARS wrote a chapter for a book³ that Alan McHughen and I edited in which he describes—without sugarcoating—his trials and tribulations in obtaining deregulation of pox-virus resistant plums. I think he's correct, particularly in terms of his criticism of formatting requirements, which can be onerous. On the other hand, he did make it through the process, demonstrating that it is doable. Dr. Scorza is a good resource, particularly for academics who don't have a regulatory staff.

- **Format for data submitted to EPA under FIFRA section 3 and FFDCA sections 408 and 409**
- **Data packages submitted to the Agency outside of this format will most likely be rejected (BPPD may never see them)**
- **This is where a consultant comes in handy!**
- **http://www.epa.gov/pesticides/PR_Notices/pr2011-3.pdf**

Figure 5. PRN 11-3 formatting.

The Pesticide Registration Improvement Act—not a policy of the agency—is a statute passed by Congress. It was put together by stakeholders, NGOs, and industry and agency representatives in 2004 (Figure 7). In its third iteration, it sets fee schedules. Companies with 500 or more employees have a particular fee schedule. For a university or USDA-ARS scientist, waivers apply. For example a PI at Texas A&M will likely be eligible for a 75 percent waiver in comparison with the company fee. If a large company applies for deregulation of a new active ingredient for first food use, the fee may be \$400,000 to \$500,000 upfront. Tables are available setting out fee schedules for different groups of

³Wozniak CA McHughen A (Eds) (2012) Regulation of Agricultural Biotechnology: The United States and Canada. New York: Springer.

pesticides, These tables also provide firm timelines. These do not define when a registration will be granted, but rather when a decision will be made, on the assumption that a full and complete data package was submitted on day one. Some registrants have expressed approval of this approach because it removes some of the uncertainty; the previous queue system was inefficient.

➤ **The Pesticide Registration Manual ("Blue Book")**

<http://www.epa.gov/pesticides/bluebook/>

- Chapter 20: Forms & How to Obtain Them
- Chapter 21: Submitting Applications, Contacting EPA
- Chapter 11: Tolerance Petitions
- Appendix A: Guidance Documents
- Appendix B: Examples of Registrant Documents
- Appendix C: Forms Overview Table
- Appendix D: Examples of Completed Forms

Figure 6. Where to begin.

➤ **Statute that directs EPA to collect fees to regulate and register pesticides**

➤ **Establishes a decision* Time Frame**

- Fee Category Determines Fee & Time Frame

➤ **Assumes the Application is Complete:**

- Administrative Documents
- Data Requirements are Addressed
- Fees are Paid, or
- 25% (or 50%) of Fees Paid if Requesting a Fee Waiver

* Not necessarily a registration!

Figure 7. Pesticide Registration Improvement Act (PRIA 3).

SUMMARY

Consultations can be very informal. It's best if the applicant can visit EPA, but, otherwise, the initial consultation may be achieved by telephone, possibly a conference call, or email (Figure 8). Even a pre-submission meeting will be treated as confidential. At no cost, meeting minutes are generated, laying out what was discussed, what was agreed upon, what is left open, *etc.*, which initiates the process. It is advisable to have consultations early on because they may lead to beneficial alterations, for example in terms of generation of less data or discovery of a waiver rationale. As mentioned, the formatting requirements are mandatory, and assistance of a consultant is recommended. However, absence of a consultant should be not considered as a deal breaker. Others have achieved deregulation, and EPA staff—regulatory specialists—are there to assist.

- **Early consultation before submission of application is encouraged**
- **“Pre-submission” meeting(s) - confidential**
- **Determination of applicable data requirements needed early on in process**
- **Formatting requirements are mandatory and a consultant is recommended for formal submissions to the Agency**

Figure 8. Summary—navigating EPA.

Several websites are available for guidance; they are continuously updated and improved (Figure 9). Kimberley Nesci or I may be contacted to set up a pre-submission meeting or to answer other questions.

- <http://www.epa.gov/pesticides/biopesticides/regtools/biotech-reg-prod.htm>
- http://www.epa.gov/scipoly/sap/meetings/2000/october/brad3_enviroassessment.pdf
- http://www.epa.gov/pesticides/biopesticides/reg_of_biotech/eparegofbiotech.htm
- <http://www.epa.gov/scipoly/sap/meetings/2009/022509meeting.htm>
- http://www.epa.gov/oppbppd1/biopesticides/pips/pip_list.htm
- EPA – Kimberly Nesci, Branch Chief, Microbial Pesticides
(Nesci.Kimberly@epa.gov)
 - Chris Wozniak, Biotechnology Special Assistant
 - » (Wozniak.Chris@epa.gov)

Figure 9. Sources of assistance.



CHRIS WOZNIAK received his training in plant pathology and life sciences at the University of Nebraska at Lincoln, where his research efforts focused on cell differentiation and morphogenesis in *Sorghum bicolor*. He worked in David Galbraith's laboratory at UNL, developing insect-resistant cotton and with Lowell Owens at the USDA-Agricultural Research Service, Beltsville, developing transformation protocols in sugarbeet. He then joined the Sugarbeet Research Unit of the USDA-Agricultural Research Service in Fargo, ND, where he worked on biological control of an insect pest.

After 18 years in plant-science research, he entered the world of regulatory science at the US Environmental Protection Agency Office of Pesticide Programs. He performed risk assessments of microbial and plant-based pesticides, particularly in the areas of human health and environmental consequences of gene flow.

For four years, Dr. Wozniak served as the national program leader for Food Biotechnology and Microbiology at the USDA's Cooperative States Research, Education and Extension Service. While at CSREES, he directed two competitive grant programs in the areas of microbial food safety and environmental risk assessment for products of biotechnology.

In 2008, he rejoined the EPA as a biotechnology special assistant in the Office of Pesticide Programs, focusing on issues of biotechnology policy, interagency coordination of biotech regulations, and environmental risk assessment of plant-incorporated protectants.

Reflections on the Past, Present and Future of USDA's Regulation of Agricultural Biotechnology

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In this presentation, I will include a retrospective, breaking things down into arbitrary timeframes. I am defining the past as from the 1950s through 1992, the present from 1993 to 2013, and the future from today onward (Figure 1).

- 
- **The Past: 1950s – 1992**
 - Promise and concerns
 - Regulation vs Guidance
 - **The Present: 1993 – 2013**
 - Increased implementation demands
 - Increased public engagement
 - **The Future: 2013 →**
 - Guiding principles
 - Considering diverse viewpoints

Figure 1. Past, present and future.

PAST

Not long ago, DNA was identified as heritable material, and last year—2012—we celebrated the 40th anniversary of the creation of the first recombinant-DNA organism, a bacterium (Figure 2). The scientific community came together in the mid 1970s, and as a group said:

Let's take a break. Let's look at the issue of safety. Let's make sure that this new technology can be used safely.

They called on the National Institutes of Health to develop guidelines for the safe use of recombinant-DNA organisms in contained facilities; the guidelines were promulgated in 1976. The first commercial product from a recombinant organism was human insulin, marketed in 1980. And, in 1983, a recombinant plant was first described in the literature. I remember hearing about this as a beginning plant pathologist, and thinking that it would be a great tool for breeders as it touched upon the bedrock principle of using the best possible genetic basis to obtain resistance to pathogens.

The term “modern biotechnology” typically includes recombinant-DNA organisms (Figure 2). In the United States and other countries, cell-fusion refers to combination of distantly related organisms; however, relatively little work has been done in this area. The note at the foot of Figure 2 is a reminder of the varied terminology that is used. Even the federal agencies use different terms, therefore one system cannot be laid on top of another, nationally or internationally. Internationally, “living modified organism” (LMO) is sometimes used, *e.g.* within the Cartagena Protocol. Everyone is familiar with GMO and “transgenic” is commonly used, whereas GEO seems almost archaic

➤ **Recombinant DNA techniques (recDNA)**

- 1950s, DNA role in heredity
- 1972, first recDNA organisms (bacteria)
- 1976, guidelines from National Institutes of Health (USA)
- 1980, first commercial product (insulin)
- 1983, first recDNA plant

➤ **Cell fusion of distantly related organisms**

Note: Definition of terms is inconsistent:

- recDNA, GMO, GEO, LMO, transgenic

Figure 2. Techniques of modern biology.

In my work for a regulatory agency, not only has my background in science been of utility, but so have my high-school civics classes. The combination has been essential in understanding the legal context within which the system operates. A necessary part of this is technical practicality; regulations must be enforceable. Of course, safety is a fundamental

consideration and public policy has a role. Some countries enact public policy aimed at promoting innovation or at tying their regulatory approach into a national system that assists development of the agricultural or the science and technology sector. And in recent years, international obligations have come into play increasingly.

The Coordinated Framework for Regulation of Biotechnology—proposed in 1984 by the White House Office of Science and Technology Policy and finalized in 1986—spells out the basic federal policy for regulating the development and introduction of products derived from biotechnology (Figure 3). This regulatory policy framework was developed to ensure safety of the public and to ensure the continuing development of the fledgling biotechnology industry without overly burdensome regulation. It applies as much today as it did in 1986: in essence, the employment of these techniques does not, in and of itself, raise safety concerns. Also, federal laws, already enacted, cover any safety issues, and, if further regulation is needed, it should be based on the best available scientific information. Furthermore, applications for deregulation should be dealt with on a case-by-case basis.

- The safety risks of GE organisms are not fundamentally different from safety risks posed by non-GE organisms with similar traits.
- The existing laws provide adequate authority.
- Regulation should be science-based and conducted on a case-by-case basis.

Figure 3. Coordinated Framework (1986):
Federal role in the safe use of biotechnology.

APHIS regulation of GE organisms is pursuant to the Plant Quarantine Act (PQA) of 1912 and the Federal Plant Pest Act (FPPA) of 1957. The original acts, which had nothing to do with genetically engineered organisms, were set up so that the federal government would have the ability to prevent plant pests—insects and pathogenic organisms—from coming into the country and moving interstate. These statutes were rolled together, along with the Noxious Weed Act, into the Plant Protection Act of 2000. After vigorous debate—should the USDA operate under federal regulations or operate under an advisory system akin to the National Institutes of Health Guidelines—it was decided to go with a legally binding system under regulations, put in place in 1987.

Every regulation basically comes down to two parts: the item regulated and the activities of that item, which, under APHIS regulations (7CFR Part 340) is termed a “regulated article,” which has two parts to the trigger (Figure 4). The plant has been modified or produced using recombinant-DNA technology to modify the organism; and there has to be a possibility that the genetically engineered plant has a pest risk associated with it. In other words, if a recombinant DNA technique has been employed to modify an organism,

- “Regulated articles” (7 CFR part 340)
 - If the organism has been altered or produced through genetic engineering, **and**
 - If there is a possibility that the GE organism could be a plant pest, i.e.,
 - Donor, recipient, or vector organism is a plant pest
 - “Plant pest” is defined by statute
- Is my GE organism a regulated article?
 - www.aphis.usda.gov/biotechnology/am_i_reg.shtml

Figure 4. What does APHIS-BRS regulate?

and the donor organism, the recipient organism or the vector agent is a plant pest, then the resulting genetically engineered organism is called a “regulated article.”

Over the years, people contacted us: “I’ve read the regulation and still don’t understand whether I have a regulated article.” A few years back, APHIS set up a website (Figure 4) that gives instructions on how to put together a letter of enquiry regarding a proposed or actual organism. No risk assessment involved. The feedback from APHIS is in terms of, “Yes, that meets the definition of a regulated article,” or “No, it does not meet the definition of a regulated article.” Fourteen such letters and APHIS’s responses are posted on the website. This has been an eye-opener for some who thought that if genetic engineering techniques are involved, the item automatically falls under the regulations, which is not the case.

Figure 5 shows the activities that require authorization: importation to the United States; movement from state to state (not intrastate movement); and/or release into the environment. One of two authorization mechanisms may be applicable: the original permitting procedure that has been part of the regulation since 1987; the notification procedure which was introduced in 1993 to provide a more streamlined approach. Both procedures set out how the regulated article is to be authorized for importation, interstate movement and release into the environment.

PRESENT

Twenty years, 1993–2013, is a generous time span for “the present” (Figure 1). In 1993, we added something that the original regulations had no provision for: the commercialization of genetically engineered plants. A farmer could not be expected to obtain permits and notifications every time (s)he moved genetically engineered seed or planted

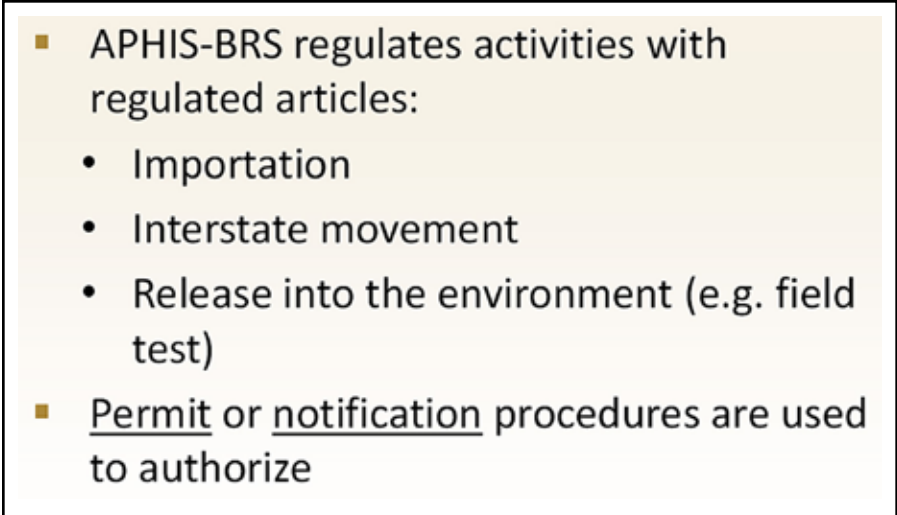
- 
- APHIS-BRS regulates activities with regulated articles:
 - Importation
 - Interstate movement
 - Release into the environment (e.g. field test)
 - Permit or notification procedures are used to authorize

Figure 5. Introduction of regulated articles.

a genetically engineered crop. We established a procedure whereby someone can petition us, in writing, for review to request that their genetically engineered organism should no longer be a regulated article because it doesn't pose any plant-pest risk. Also, the US public was given the opportunity to be involved in these reviews, which is unusual. The dossier of information submitted to the agency supporting the contention that the genetically engineered organism is not a plant pest is available for public review—and comment—before final APHIS determination.

These petitions involve two evaluations by APHIS. We make a risk assessment—as a stipulation of the Plant Protection Act—to answer the question: *Does the genetically engineered organism pose a plant-pest risk?* And we make an environmental assessment—as a stipulation of the National Environmental Policy Act (NEPA, signed by Richard Nixon in 1970, setting standards for federal agencies to appraise the significance of environmental impacts that might arise from their decisions¹). Under NEPA, the public again has the opportunity to provide input. This does not determine the agency's decision, but it does inform the decision-making process.

To date, APHIS-BRS has made determinations of non-regulated status in response to over 90 petitions, comprising 16 plant species (Figure 6). Once non-regulated status is granted, the petitioner's obligation under the regulation is finished: there is no license; there is no permit; nothing needs to be reviewed. Progeny derived from the organism through traditional plant breeding also has non-regulated status. For example, hundreds of varieties have been developed from the first glyphosate-tolerant soybean ("HT" in Figure 6) to receive non-regulated status from us in the 1990s. Likewise, hundreds of varieties

¹Back then, the decisions had nothing to do with genetically engineered organisms; they applied to federal agencies responsible for building bridges, dams, roads, *etc.*

that have been developed from the early *Bt* corn genotypes (“IR” in Figure 6), with no obligation to apply for deregulation. Our statute is unrelated to commercialization; it strictly deals with safety issues. Some genetically engineered plants under regulation are actually being used as sources for commercial purposes, but all are being grown under permits.

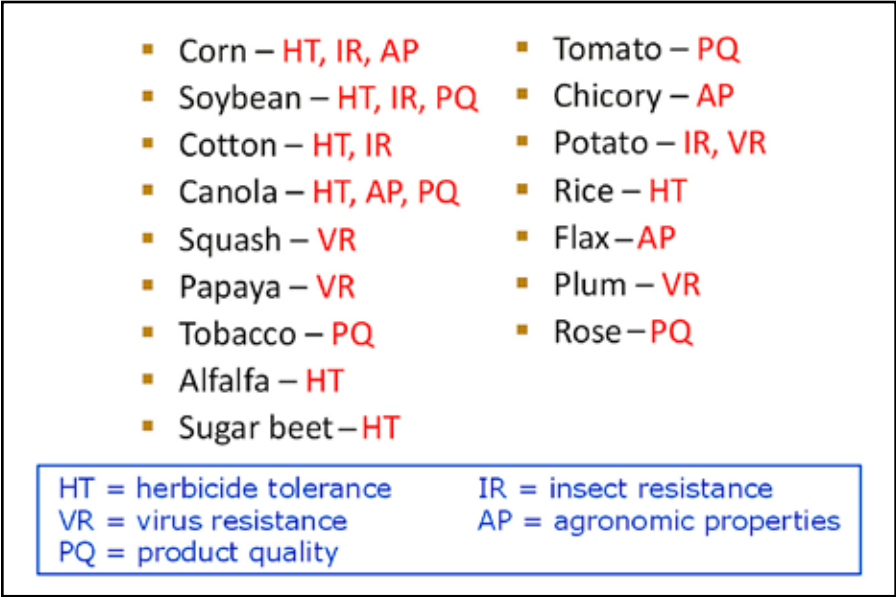


Figure 6. Genetically engineered species with non-regulated status under 7CFT part 340.

Commercialization is not under APHIS’s authority. Whether a product is commercialized is market-driven. The left column in Figure 6 shows products that are on the market as of June 2013, including the high-profile cases of herbicide-tolerant alfalfa and sugar beet, and less well known tobacco with reduced nicotine. Dennis Gonsalves’s² papaya is also in the left column, And we have everything from insect resistance (“IR”) and drought tolerance (“AP”) in corn, through herbicide tolerance in canola (“HT”) to high oleic acid content in soybean (“PQ”). The right column includes the FlavrSavr[®] tomato and another slow-ripening high-solids tomato. Male-sterile chicory (“AP”), sometimes called radicchio—developed in Belgium in the mid-1990s—has non-regulated status, but does not have consumer approval in Europe. Several herbicide-tolerant rice lines have been through the system, but commercialization is pending, subject to approvals in other countries. The blue rose (“PQ”) and Ralph Scorza’s plum³ (“VR”) are also in the column on the right; they are gearing up for commercial release of the virus-resistant plum. Some others are on track for commercialization .

²Pages 37–46.

³Page 136.

Recent APHIS-BRS Initiatives

In 2007, we initiated a voluntary compliance-assistance program, with early input from large companies, medium-size companies and public research institutions. An extensive effort in recent years has examined the petition process to make it more efficient. Over the years, we went from a six-month timeframe for completing reviews, to where it was taking up to several years. Petition-process improvement was put into place in 2011. And in 2008 we proposed amending the regulation. In the United States, a regulation is proposed and followed by a public-comment period, after which the regulation may be finalized. In this case, after announcement of the initial proposal, 66,000 comments were received and are still being appraised.

- Scientific integrity
- Public participation
- Communication
- Flexibility
- Risk assessment and risk management
- Coordination
- International cooperation
- Benefits of regulation should justify costs
- Promote innovation while advancing protection goals (health, environment, safety)
- If no significant issues identified, consider not regulating
- Develop performance based regulatory approaches that are predictable and flexible in the face of fresh evidence

Figure 7. Guiding principles for regulating new technologies.

FUTURE

In 2011, a memorandum was issued by the White House Office of Science and Technology Policy in conjunction with the Office of Management and Budget and the US Trade Representative's Office—frequently referred to as the Holdren memo—titled *Principles for Regulation and Oversight of Emerging Technologies*. Although it is not aimed at biotechnology alone, it is similar in tone and emphasis to the *Coordinated Framework for Regulation of Biotechnology*, *i.e.* favoring innovation, having enough regulation as necessary and to also consider that there may be no need for regulation.

Figure 7 shows key principles espoused in the Holdren memo. International cooperation is becoming increasingly important, especially in the biotechnology area. Again, the benefits of a regulation should justify the costs it incurs. Are regulations the best approach? How much leeway is in the system? Technically, if you set up a class of things that are regulated, can you distinguish them from counterparts that are not regulated? Safety, of course, comes into play as part of public policy. The Holdren memo is an example of public policy that sets out international obligations.

The Sanitary and Phytosanitary Agreement under the WTO, which came into being in 1995 says, in essence: “In the absence of good scientific evidence that demonstrates harm to plants, animals or to humans, we should not restrict trade.” This lens may be applied to the regulatory systems in the United States and elsewhere.

The Secretary of Agriculture's Advisory Committee on Biotechnology and Agriculture has, over the past two years, taken up the issue of coexistence. Although this has to do with crops after they're out from under our regulatory system, APHIS-BRS has been involved in helping to bring stakeholders together for on-going discussions.

Figure 8 provides our website and means to obtain stakeholder-information updates via email.

- **USDA-APHIS-BRS on the web:**

- http://www.aphis.usda.gov/biotechnology/brs_main.shtml

- **Become a BRS Stakeholder:**

- Sign up for automatic news and information:

- <http://www.aphis.usda.gov/biotechnology/index.shtml>

- Click on the red envelope at the bottom right corner of the page



Figure 8. For more information.

DAVID HERON is assistant director of Policy Coordination Programs of Biotechnology Regulatory Services, the unit responsible for implementing the biotechnology regulations of the US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS). His primary responsibilities include the development of coherent and coordinated national and international policies, risk assessment, regulatory analysis, communication, and domestic and international regulatory capacity building in agricultural biotechnology.

Dr. Heron has served in the APHIS biotechnology regulatory program since 1991, with the exception of a year during which he served as task manager with the United Nations Environment Programme for eight country projects on the implementation of national biosafety frameworks (Bulgaria, Cameroon, China, Cuba, Kenya, Poland, Namibia and Uganda). He received his BA in biology from Gettysburg College and his PhD in plant pathology from the University of Missouri-Columbia.

Ensuring Food and Feed Safety: US Food Law and FDA's Biotechnology Consultation Process

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A key aspect of the authority for regulating genetically engineered crops is the legal basis of that authority. For example, in contrast to what some people think, the Food and Drug Administration (FDA) cannot make consultation mandatory, because there is no law to permit it. In 1992, FDA published an article in the *Federal Register*—*The Statement of Policy: Foods Derived from New Plant Varieties*—in which was discussed its legal framework for considering new plant varieties as a whole, including genetically engineered varieties. The article's focus was chiefly on elements already in the Food, Drug, and Cosmetic Act (FD&C Act), and it explained the agency's thinking about safety and regulatory issues pertaining to new plant varieties, based on several parts of existing food law.

The first issue is adulteration, the second is food additives, and the third is labeling (Figure 1). There are two basic elements to US food law. The first is the responsibility of purveyors—which include crop developers, farmers, and manufacturers—to ensure that the foods they market are safe, wholesome, and comply with all applicable legal and regulatory requirements. The second element is what FDA does to enforce the law, using regulatory tools to remove unsafe or illegal foods and ingredients from the marketplace. These include seizures, recalls, and denial of entry of food from abroad.

We have a program to help developers ensure that food from new plant varieties is safe and complies with laws and regulations. Three legal requirements are applicable.

- Safety: The food is as safe as that generated from traditionally bred varieties.
- Labeling: The food labeling is truthful and not misleading.”
- Additives: Is premarket review required?

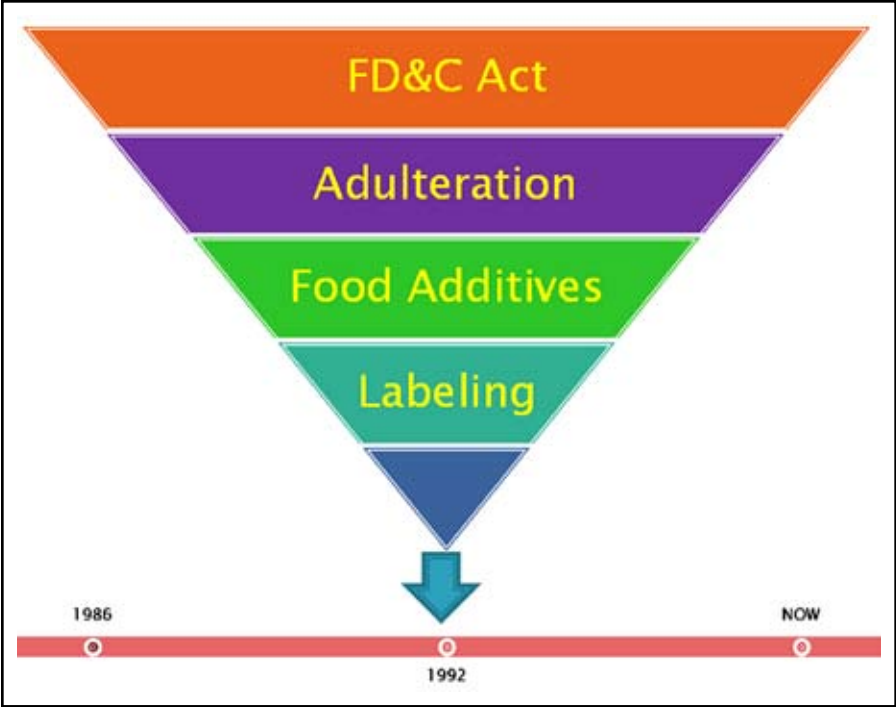


Figure 1. FDA's legal framework for foods from new plant varieties.

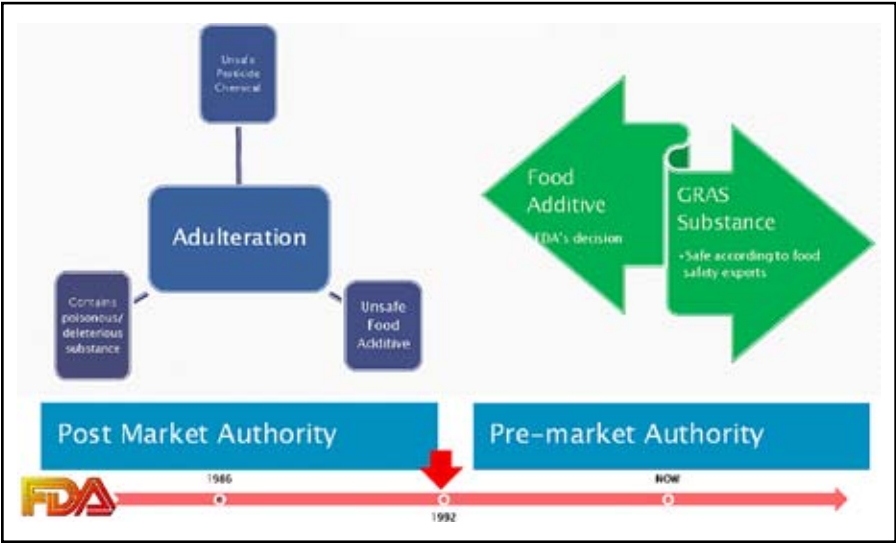


Figure 2. FDA's authority: the FD&C Act.

FDA'S AUTHORITY

There are two basic elements to FDA's authority. The first is post-market authority (Figure 2), under the adulteration provision of the FD&C Act, which, generally, applies to whole foods. A food is considered adulterated if it contains a poisonous or otherwise deleterious substance known to harm humans or animals, if it contains an unsafe food additive, or if it contains an unsafe pesticidal chemical. The second element is FDA's premarket authority governing food additives, unless data show that they are generally recognized as safe ("GRAS") by qualified experts in their intended use.

Under what circumstances would a food additive be present in a genetically engineered plant? It would be a new protein or the product of a new protein for which safety information is not publicly available or widely accepted. Accordingly, FDA would require a review before marketing. So far, the only example of a food additive in a genetically engineered plant was the NPTII enzyme used as a selective marker in the FlavrSavr tomato. At the time Calgene submitted its food-additive petition, there was no experience with using proteins of this type in food.

LABELING

According to the "misbranding" part of the FD&C Act, a label on a food must be truthful and not misleading. A label must be changed if a meaningful difference is created by conferring a change in a food; it must be called something different. To date, the best examples are modified oil crops, *e.g.* high oleic acid soybean and stearidonic acid soybean.

1992 POLICY

In summary, the 1992 policy considers whether the product in question is as safe as other foods. It provided guidance to industry via decision trees and includes a suggestion that developers consult with FDA early in the development process, so that potential issues may be identified before they become problems.

CFSAN AND CVM

Submissions to FDA are evaluated by two centers for different uses. Safety of use in human food is evaluated by the Center for Food Safety and Applied Nutrition (CFSAN), whereas the Center for Veterinary Medicine (CVM) evaluates safety of use in animal feed. Again, we advise early consultations at FDA to advise us of what you are doing, then return to the lab to run tests for potential toxicity, allergenicity and antinutrient content, and potential for bioavailability alteration. This is followed by submission of a dossier—hopefully not too lengthy—describing why the use of the plant as food or would be safe and legal.

What are the issues? Regarding safety, there's the potential for toxicity, the potential for allergenicity, and for changes in levels of anti-nutrients and in bioavailability. Regarding regulatory considerations, there's the question of whether a new substance is an unapproved food additive or GRAS, or whether there's a meaningful change requiring a new common or usual name.

In essence, we ask people to tell us their story—about their new plant variety and why it's safe for food use. As for FDA's role, we recognize that there's widespread variation in plants in nature, including among domesticated varieties, affected by environmental conditions and the genetic background (Figure 3). We have developed a process whereby we evaluate final submissions and if there are aspects we don't understand, we will seek clarification. We then develop our own document, and conclude by sending a letter. We mail the letter to the submitter and place a memo on our website—a scientific evaluation that establishes whether the new variety is as safe as those already in the marketplace.

We added a new piece in 2006. When preparing for field trials with a protein that hasn't been used before, our early food-safety evaluation (Figure 4) is worthy of consideration. This guidance is termed a “new protein consultation” (NPC). If a new protein is neither toxic nor allergenic, then it would be considered safe for field testing and FDA would not be concerned if low levels appeared inadvertently in the marketplace.

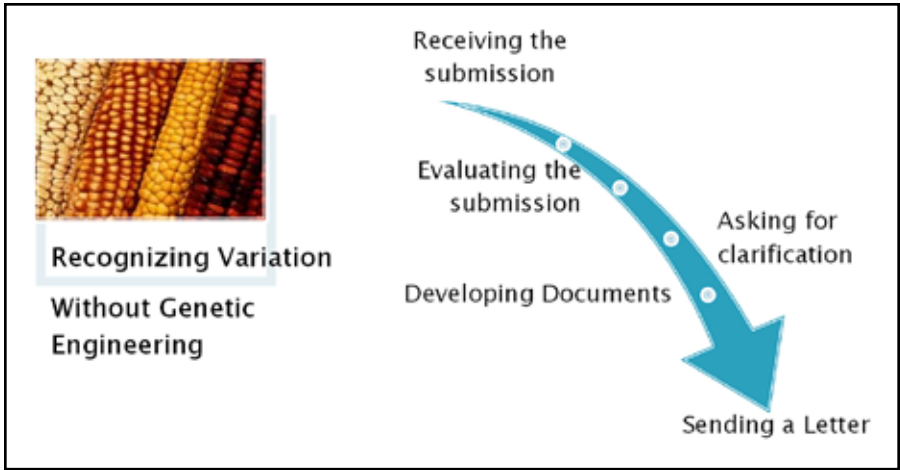


Figure 3. Consultation procedures: FDA's role.

SAFETY ASSESSMENT

As far as safety assessment is concerned, we understand that agronomic and quality issues will eliminate some lines from consideration at the very beginning of the process (Figure 5). We need to have information on new substances, including identity and source, using the weight-of-evidence approach. And we need to look at composition, and perhaps at some agronomic aspects. The intended effects must be clarified in terms of overall effects on the food and compositional changes. And, finally, unintended effects may be important. Does the insertion result in expression of (a) new or altered protein(s), or even fusion proteins? Are there unanticipated actions of a new enzyme on other components within the plant?

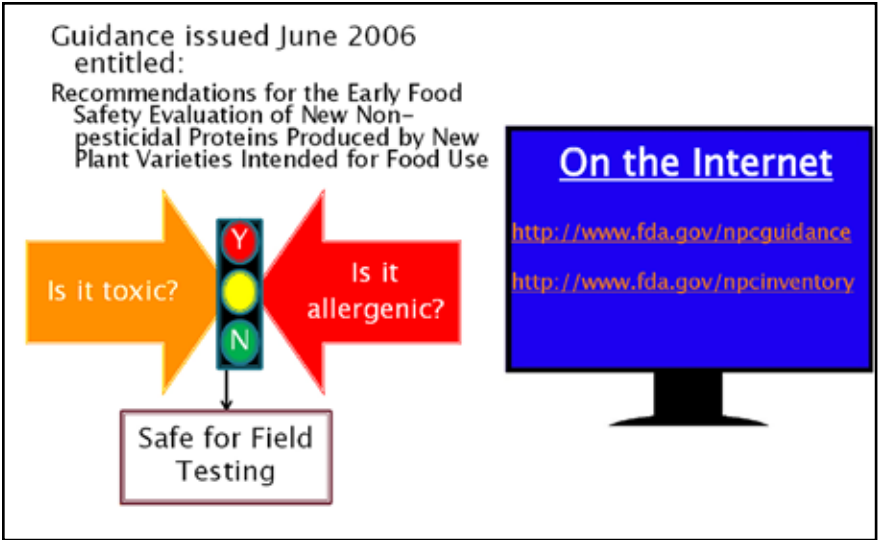


Figure 4. Early food-safety evaluations (NPCs).

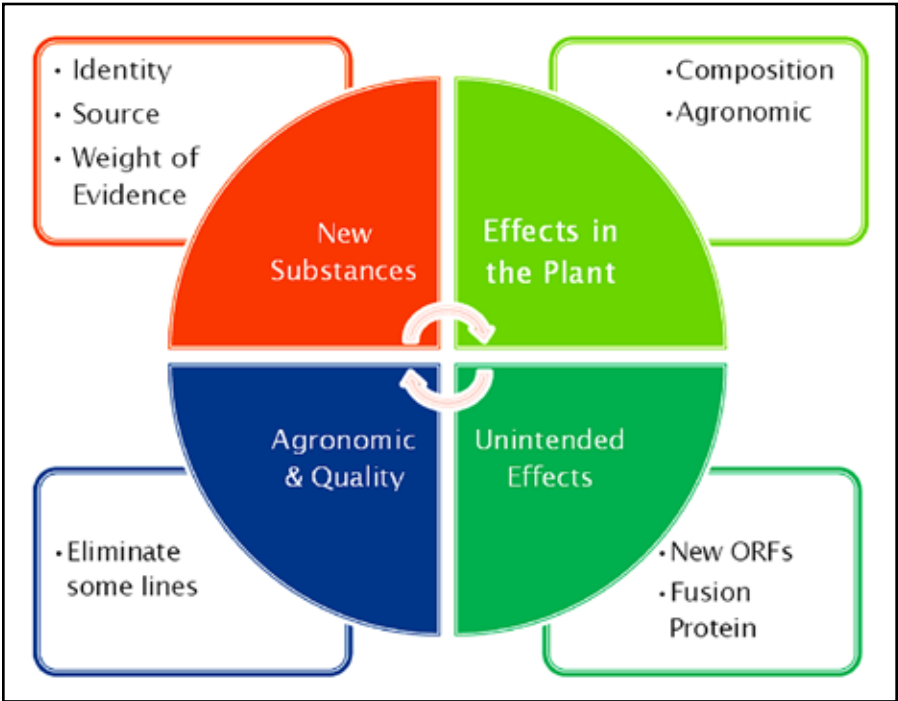


Figure 5. Safety assessment–1.

For safety assessments, three basic components are applicable (Figure 6). Genetic analysis focuses on stability and unintended effects. Chemical and nutritional analyses focus on dietary impacts and toxicant levels. And allergenicity and, to a lesser degree, toxicity are assessed. Resources for use in safety assessments can be pooled from the following sources:

- The Statement of Policy on FDA's website.
- The Codex Alimentarius guidelines.
- Guidelines set out by the Organization for Economic Cooperation and Development (OECD).

We have certain flexibility about format and how the necessary information is presented to us.

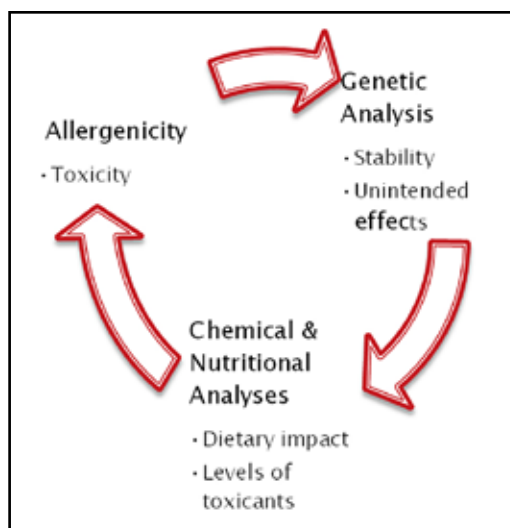


Figure 6. Safety assessment–2.

The safety of genetically engineered plants for food and feed is judged using a case-by-case approach. Generally, the genetically engineered plant is compared with a closely related conventionally developed plant, with the focus on new substances, *i.e.* toxicants, anti-nutrients, allergens and toxins. Bioinformatics are used to address the possibility that unintended new proteins are likely to be expressed, and if so, are they safe? The sequences of new proteins are compared with the sequences of known toxins, allergens and anti-nutrients.

For the molecular assessment, we require several pieces of information (Figure 7):

- Data showing which portions of the introduced DNA have been incorporated into the plant's genome.
- Confirmation that there's no vector backbone, with examination of the fidelity of insertion of the construct.

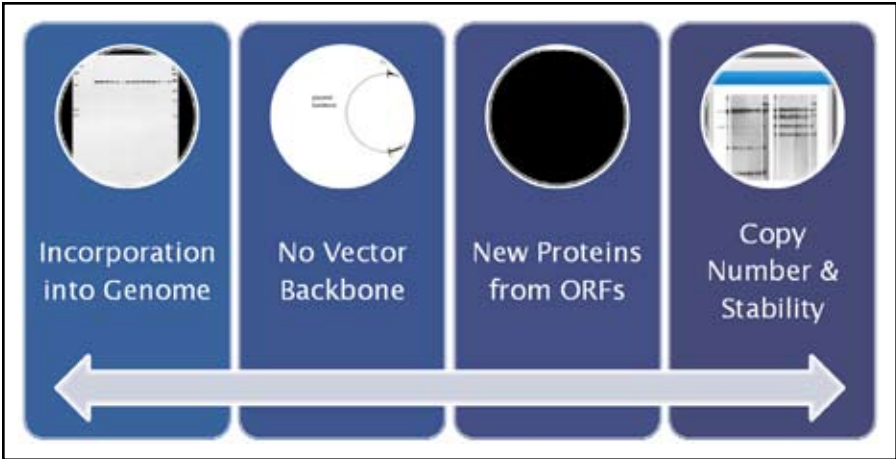


Figure 7. The molecular assessment.

- Evidence that no unintended proteins resulted from open reading frames. Ordinarily, that's based on bioinformatic analysis of the junction sequences of the insert.
- Information about copy number and stability, using genomic DNA blots or other appropriate technologies.

Next, compositional analyses are generally performed on field tests at multiple sites and usually over two growing seasons. The objective is to ensure that nutritional value is conserved, by comparing the new genetically engineered variety with a related control and/or a similar entity in the marketplace. Figure 8 illustrates the process for row crops. Key nutrients comprise proximates, *i.e.* fatty acids, fibers, amino acids, and vitamins and minerals. Again, we look at anti-nutrients, endogenous toxicants and endogenous allergens. For other types of crops, the analyses may be less comprehensive; in the case of fruit, the analyses usually comprise mostly fiber and sugar.

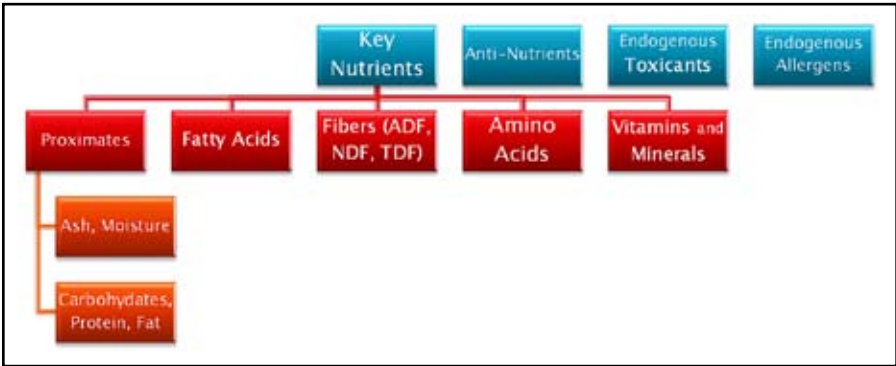


Figure 8. Compositional analyses.

EXPERIENCE TO DATE

Corn, cotton, soybean, and canola have been the focus of most of our consultations. We have seen many varieties of these crops. Traits that we’ve covered can be classified as: herbicide tolerance, virus and insect resistance, altered oil composition, male sterility, delayed ripening, other altered composition, and agronomic changes (Figure 9).

As for the types of traits, we can group them in three basic categories (Figure 10). Both EPA and FDA have roles to play in assessing plant-incorporated protectants (PIPs).

Trait	Crops
Herbicide tolerance	alfalfa, canola, corn, cotton, soybean, sugar beet, creeping bentgrass, flax, rice
Virus Resistance	Squash, plum, papaya
Insect Resistance	corn, cotton, potato, soybean, tomato
Altered composition oils	Soybean, canola
Male Sterility	Corn, canola, radicchio
Delayed ripening	Tomato, cantaloupe
Altered composition	Corn (increased lysine) Canola (reduced phytate)
Agronomic changes	Corn

Figure 9. Traits and crops evaluated by FDA.

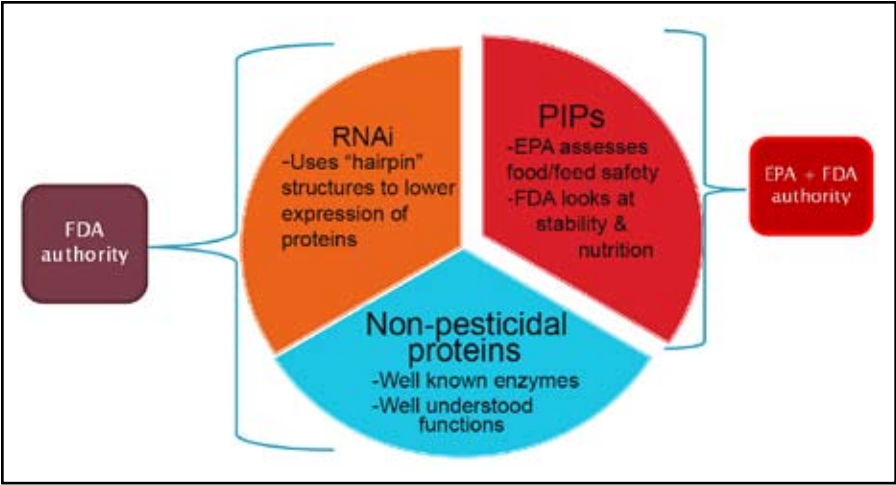


Figure 10. Types of traits.

Generally, FDA looks at stability and nutritional composition, whereas EPA looks at human and environmental safety via genomics and proteomics. For non-pesticidal proteins, FDA alone looks at food and feed safety. And FDA has had some submissions that utilize RNA inhibition.

RISK COMMUNICATION

Regarding risk communication, we try to be transparent to the degree that the law allows. Our inventory is available on the Internet (right side of Figure 11). If something is required of FDA that is not available on the Internet, a Freedom of Information Act request may be submitted. Also, we are happy to communicate directly via email, conventional mail, or by telephone. Figure 12 provides a list of resources; our main page is www.fda.gov/geplantfoods.

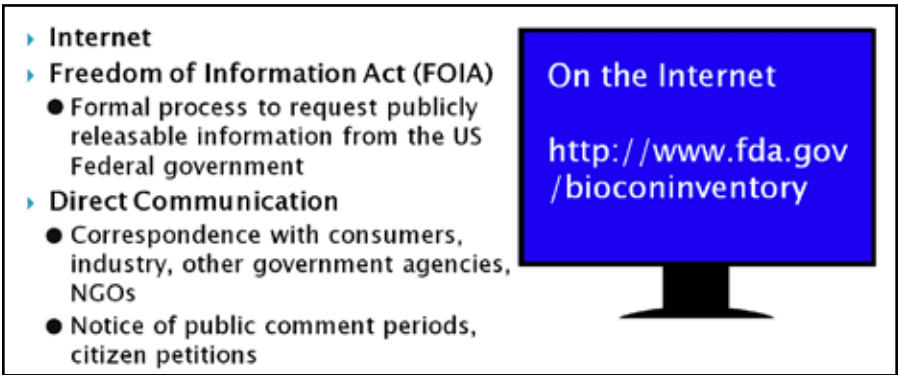


Figure 11. Transparency.

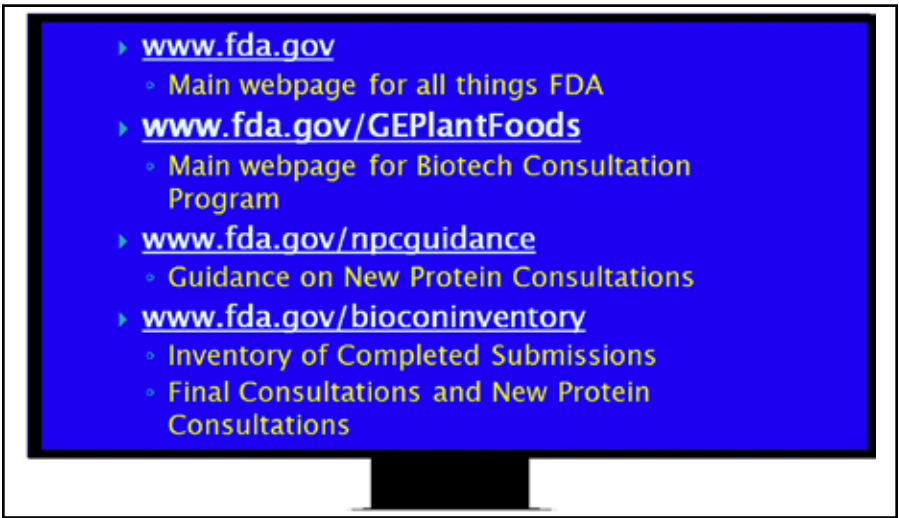


Figure 12. FDA's Internet resources.

IN CONCLUSION

Our safety evaluations are based on the premise that genetically engineered plants are as safe as their traditionally bred counterparts. We encourage developers to engage with us prior to marketing, and we communicate with our sister government agencies and international groups to ensure that we're using both the best science and the best practices. We understand that, as science evolves, we will see new technologies and new traits; however, we expect that the policy that was developed in 1992 will remain sufficiently flexible and broad to accommodate them.



ROBERT MERKER received his bachelor's degree in microbiology from the University of Illinois at Urbana-Champaign, and a PhD in microbiology from the University of California, Davis. After postdoctoral studies at the University of British Columbia and UC-Davis, he joined the Food and Drug Administration in 1991, where he did research on the outer surface of *Listeria monocytogenes*, acid tolerance in *Yersinia enterocolitica*, and the food safety of apple-cider production. In 2000, he became a consumer safety officer in the Office of Food Additive Safety.

He participated in the working group for the development of a *Codex Alimentarius* "Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms." He also has worked on a wide variety of biotechnology-related issues for FDA, and was a member of an interagency task team that has developed and maintains a joint Internet site for government information about regulation of the products of modern biotechnology.

Dr. Merker was selected as a supervisory consumer safety officer in the Division of Petition Review in the Office of Food Additive Safety in July 2007, and moved to the Division of Biotechnology and GRAS Notice Review in 2010, where he supervises several regulatory and environmental specialists. He oversees FDA's Consultations on Food from New Plant Varieties.

The Canadian Regulatory Process for Plants with Novel Traits

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In this presentation, I will represent not only Plant Biosafety Office of the Canadian Food Inspection Agency (CFIA), but also Health Canada and the Animal Feed Division within the CFIA.

Canada differs from the United States in that it regulates novelty. We regulate novelty under three different acts applicable to three different groups: novel feed, novel food and novel plant assessments. The first is the *Seeds Act and Regulations*. The group that I represent—the Plant Biosafety Office—is responsible for the environmental authorization of plants with novel traits. A plant with a novel trait (PNT) is defined as:

...a plant into which a trait have been intentionally introduced and where the introduced trait is both new to cultivated populations of the species in Canada and has a potential to affect the specific use and safety of the plant with respect to the environment and human and animal health.

Under the *Food and Drugs Act and Regulations*, a novel food is defined as:

...a substance, including a microorganism, that does not have a history of safe use as food, a food that has been manufactured, prepared, preserved or packaged by a process that has not been previously applied to that food and causes the food to undergo a major change.

My Health Canada counterparts often use the example of high-pressure processed ham as an example of a novel food because that's the process side, but products of novel plants are also considered novel foods. Under the *Feeds Act and Regulations*:

...only feed ingredients that have been approved and evaluated by the Animal Feed Division may be used in livestock feeds; approved ingredients are listed in Schedules IV and V of the Feeds Regulations. Any feed ingredient that is new (i.e. not listed in the Schedules) or has been modified such that it differs from conventional parameters, is required to undergo a premarket assessment. This concept applies to all novel feeds, including those derived through biotechnology.

Many entities, including microbial feed additives, are regulated under these feed regulations.

NOVELTY TRIGGERS

A PNT being assessed for unconfined release may also trigger a novel food/feed assessments by Health Canada and/or the Animal Feed Division of the Canadian Food Inspection Agency (CFIA).

A PNT is not necessarily a novel food or feed or *vice versa*. For example, genetically engineered turf grass is a PNT, but not a food or a feed. Genetically engineered timothy is a PNT, but not a novel food. And genetically engineered cotton is a novel food and feed, but not a novel plant—it does not trigger an environmental assessment—because it doesn't grow in the Canadian environment. Juice from genetically engineered citrus would only be a novel food because citrus trees don't grow in Canada and we would not expect anyone to import any citrus by-product as a feed. Therefore, the orange-juice people¹ have to deal only with Health Canada, whereas apple pumice is considered to be a feed ingredient, therefore Neal Carter² has had to go through the “feed” piece.

The basis for this is to ensure that an application is made only to the applicable group. If multiple applications are required, they should all be submitted at the same time to the applicable groups. After 2000, coordinated authorizations were ratified (Figure 1) whereby Health Canada and CFIA agreed to a no-split approval process. If multiple groups determine that a crop is novel, then the assessors work together to evaluate the product, and the authorization of the product is coordinated, usually within days of each other. This is done to minimize the potential for unapproved products to enter the Canadian food or feed supply.

To review: the Canadian process is unique. The focus is on the product, not on the process used to develop that product. Accordingly, a regulated product can be developed by any breeding process—including conventional breeding, genetic engineering or mutagenesis—and this approach allows the Canadian regulatory system to efficiently adjust to any new developments in science or plant breeding. Also, biotechnology is defined more broadly in Canada than in most other countries.

Figure 2 illustrates how the different groups come into play together under the mandatory premarket regulatory requirements for novel plant products. “Novel plant products” is the term that we use when referring to all three, but I'll use “plants with novel traits” (PNTs) because that is typically what we deal with.

¹Pages 75–85.

²Pages 87–94.

- Authorizations are co-ordinated under HC and CFIA’s “no split” approval policy (2000)
 - > Crops determined to be novel by the respective groups
 - > If multiple groups determine a crop to be novel then:
 - Assessors work together to evaluate the product
 - Authorization of the product is co-ordinated
 - > Used to minimize the potential for unapproved products to enter the Canadian environment, food or feed supplies.

Figure 1. Coordinated authorizations.

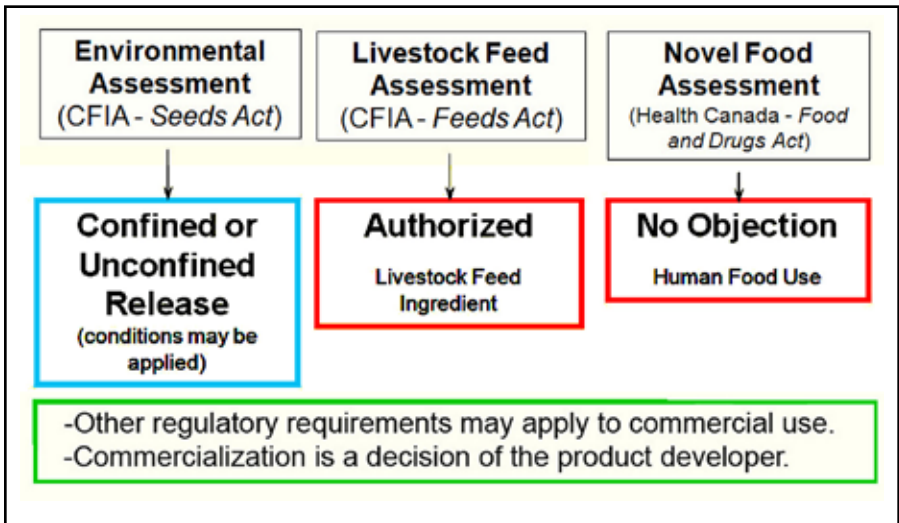


Figure 2. Mandatory pre-market regulatory requirements for novel plant products.

The environmental assessment is done by CFIA under the *Seeds Act*, with a confined or unconfined release. Confined release I’ll describe in more detail below. Unconfined release is when a product has been authorized for release into the environment and is considered as safe as its conventional counterparts. The livestock feed assessment is done by CFIA, based on the *Feeds Act*, when a product becomes authorized as livestock feed. The novel food assessment by Health Canada uses the terminology “no objection”; when they are done, they go through a food-ruling process and indicate a letter of no objection, which is posted on their web site. Other regulatory requirements may apply prior to commercial use. For instance, if the crop requires a variety of registrations in Canada, like soybeans or canola, then we have a variety of registration processes that must be completed prior to commercialization. And commercialization is always the decision of the developer.

FEED REGULATION

We are often asked why we regulate animal feed (Figure 3). Part of the reason is that, typically, the domestic animal's diet is made up of a small number of products at higher levels than we ever see in a human diet. Also, different components are consumed; humans may eat a different part of the plant from what animals eat, and no processing or different processing may be involved. Animal health and productivity impinge on the food chain and it is important that nutritional value or safety of products such as milk, meat and eggs are not affected. Assessments ensure that the feed is efficacious for its intended purpose and safe in terms of animal and human health.

Feed versus Food, consider:

- Daily feed consumption
- Limited variety
- Different components are consumed
- No processing or different processing
- Animal health and production
- Food chain (milk, meat, eggs)

Figure 3. Why regulate feed?

NOVELTY DETERMINATION

When it comes to novelty determination, it is the proponent's responsibility to characterize their plant and to self-identify to the CFIA a product requiring authorization for environmental release. We expect the developer to approach us and say, "I have a product that I think may be novel." Communication is key, and the earlier that communication takes place, the better.

The CFIA has the ultimate decision-making authority regarding regulatory status determination and reserves the right to require a proponent to provide scientific justification for determination that a plant is not a PNT. If we feel that it is and the proponent feels that it isn't, then the latter must provide justification in writing. Our assessment will be science-based and done on a case-by-case basis. Accordingly, this regulatory approach, again, is based on the product, not the process. Figure 4 shows essential questions to address whether a product is novel.

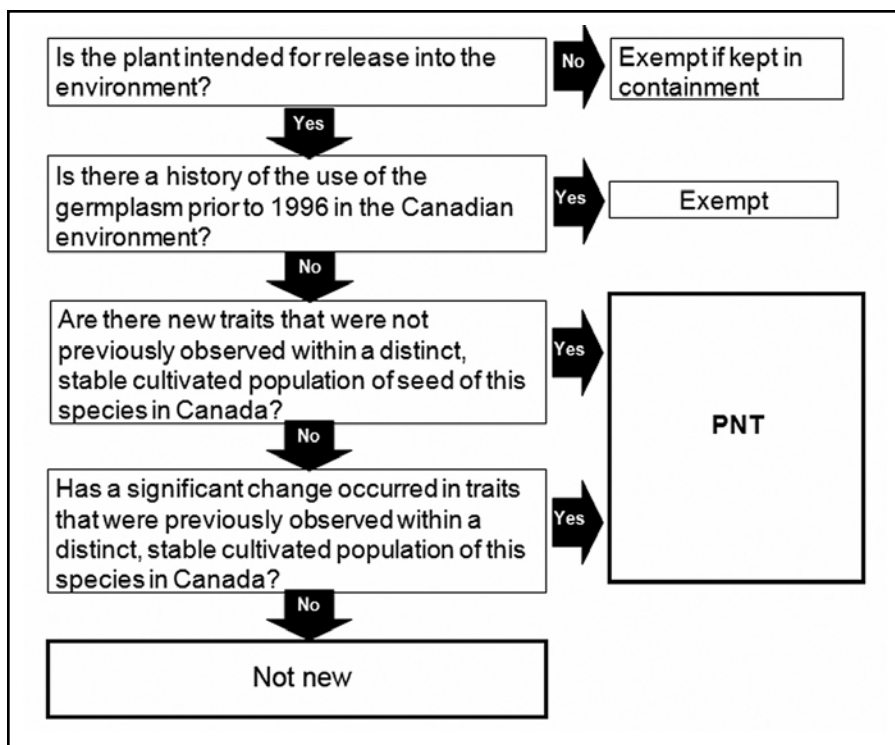


Figure 4. Regulatory approach: product not process.

Is the plant intended for release into the environment?

The CFIA does not have a regulatory requirement as long as the product is contained in a greenhouse, laboratory, *etc.*

If environmental release is intended, is there a history of use of the germplasm prior to 1996 (i.e. when the Seeds Act regulations came into effect for plants with novel traits)?

If the product was released into the environment prior to 1996, then, again, it is exempt from this process.

Are there new traits that were not previously observed within a distinct stable cultivated population of seed of this species in Canada?

This trigger may affect a conventionally bred product if it involves new germplasm containing a brand new, or very different, trait. For instance, in Canada, our list of regulated plant products includes a herbicide-tolerant wheat and a herbicide-tolerant sunflower, neither of which was developed through genetic engineering. Sometimes this causes us grief when people see "wheat" on the list, whereas wheat is not considered a living modi-

fied organism (LMO) and, therefore, in most countries is not regulated as a product of biotechnology. Because these wheat and sunflower genotypes each have a new trait, they become PNTs.

Has a significant change occurred in traits that were previously observed within a distinct stable cultivated population of this species in Canada?

If the answer is no, then it isn't new, but if it's yes, then it is a PNT.

When ascertained to be a plant with a novel trait, the next issue is whether it is of domestic or imported origin. If the latter, then an import permit policy has to be followed, on the application for which the PNT status is declared and it comes to my office—the Plant Biosafety Office (PBO)—for review. Once imported, if it is held in containment, then we would track that it stays in containment, whereas if it is to be tested in field trials, those trials would need prior approval. Along the left edge of Figure 5, “Ongoing communication with regulators,” signifies a critical aspect whereby we can help applicants to expedite the process.

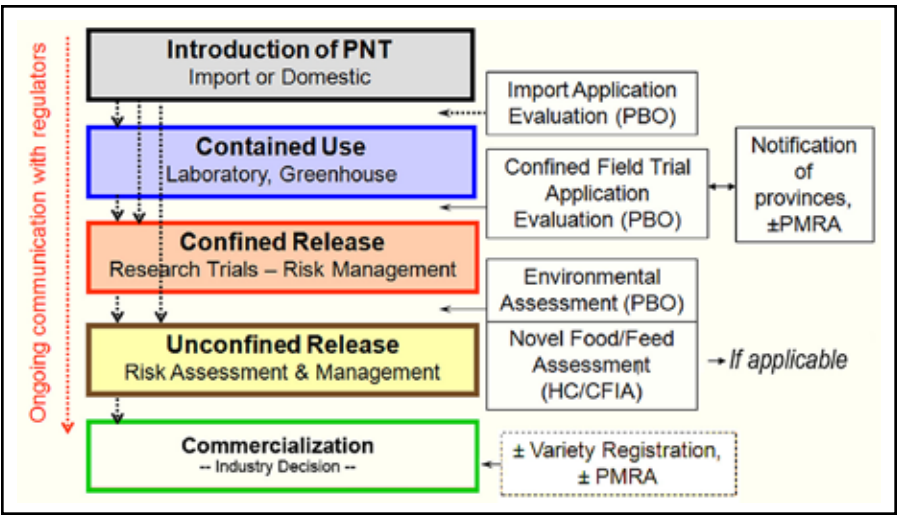


Figure 5. Regulatory pathways for PNTs.

Again, whether the PNT is imported or developed in Canada, if it stays in containment no further action is required. As soon as it is moved outside of the contained use into the confined release research trial program, then a confined field-trial application form must be submitted through the PBO, the purpose of which is to minimize risk by preventing entry into the animal and human food chains. When we receive a confined field-trial application, we notify the provinces, requesting comment in a minimum of 30 days. Therefore, our confined field-trial process takes at least 30 days. No deadline is stated on our website, but the earlier in the year that the application is received, the greater is the chance that the product will be approved for planting that year.

Many inspections are made under the confined release research program. Once the grower's data have been collected, the environmental assessment—the novel-feed, novel-food assessment piece—comes in, with the application for unconfined release, and from an environmental side, again, when unconfined release is authorized, we say that it's as safe as its conventional counterparts.

Again, commercialization is an industry decision, and if the PNT is a crop or a commodity that requires registration under the *Seeds Act*, then a variety of registrations must be completed before commercial sale of seed is possible.

ENVIRONMENTAL RELEASE OF PNTs

Risk equals hazard times exposure. A confined release is necessary when the environmental hazard is unknown or not fully characterized (Figure 6), *i.e.* the plant developer's research is ongoing, some of our questions are unanswered, and the regulatory program concentrates on environmental exposure and the evaluation and mitigation of risk.

• Risk = Hazard x Exposure

- **Confined Releases**
 - > Environmental hazard is unknown or not fully characterised
 - > Regulatory program concentrates on environmental exposure evaluation and mitigation
- **Unconfined releases**
 - > Environmental exposure of a known risk (maximum exposure is assumed)
 - > Regulatory program concentrates on environmental hazard evaluation* and stewardship, where required

*Sometimes referred to as “safety assessments” to distinguish them from quantitative risk assessments

Figure 6. Regulatory approach for environmental release of PNTs.

An unconfined release is possible when the risk is known and maximum exposure may be assumed; the regulatory program concentrates on evaluation of the environmental hazard, and we may introduce stewardship conditions that, sometimes, are referred to as “safety assessments” to distinguish them from risk assessments.

The purpose of our confined research field-trial program is to provide opportunities for plant developers to cultivate their PNTs in agronomic settings while minimizing environmental exposure. These trials are subject to conditions intended to minimize persistence and spread of the plant in the environment, and to prevent contamination of food and feed with unapproved plant material. Each trial is inspected multiple times by CFIA representatives to assess compliance with conditions, including post-harvest checks to determine that plant material has been adequately disposed of and to verify that it was produced exclusively for research purposes.

The purpose of the unconfined environmental-release program is to allow release of PNTs into the environment with limited or no restriction. It may require stewardship plans; for instance, prior to our authorizing a herbicide-tolerant crop, we require that the proponent tells us exactly how it will be managed and how development of resistance will be minimized. And for insect resistance, management requirements include refuges. The authorized products will have been assessed to be as safe as comparable products with a history of safe use. A question we ask is: “Does the addition of one or more traits change the plant’s impact on the environment in comparison to the same crop grown in the agricultural setting?” Once we have authorized a PNT, it is not handled any differently from its conventional counterparts.

We are often asked how many acres of genetically engineered crops are currently grown in Canada. It is approximately 99 percent of our canola and 97 percent of our corn, but the only way we can estimate acreage would be based on the adoption of the technologies in the various commodities.

REQUIRED SCIENTIFIC INFORMATION

Scientific information required in PNT applications includes:

- Identification and classification, comprising taxonomy, history of use and organism description
- Intended use of the PNT
- Description of the novel trait(s)
- Method used to detect the trait
- Molecular and agronomic data specific to the trait
- Optional: Participation in a public *Notice of Submission* initiative.

Regarding the optional item, the CFIA doesn’t have authority to have a mandatory comment period. We have what we call a “voluntary comment period,” in which most proponents participate. The invitation to make (a) comment(s) is a brief document—unlike what is posted in the United States—summarizing the data that we have received. We indicate that we will accept scientific comments, which only rarely are received, but the summary tells the public what we’re looking at and gives them the opportunity to tell us, typically, how opposed they are to genetically engineered technology in general.

ENVIRONMENTAL SAFETY ASSESSMENT

From an environmental perspective, we have what we consider the five main criteria or pillars of PNT environmental safety assessment; we look at the:

- Potential of the PNT to become a weed or invasive
- Potential for gene flow from the PNT to related species, the hybrid offspring of which may become a weed or be invasive
- Potential for the PNT to become a plant pest
- Potential impact of the PNT on non-target organisms
- Potential impact of the PNT on biodiversity.

Vis-à-vis the plant-pest criterion, the issue is whether the change in the plant makes it a potential sink for, say, fungal disease that could then impact neighboring crops. Regarding effects on non-target organisms, the main sources of concern expressed by members of the public are adverse effects on honeybees and monarch butterflies.

FOOD- AND FEED-SAFETY ASSESSMENTS

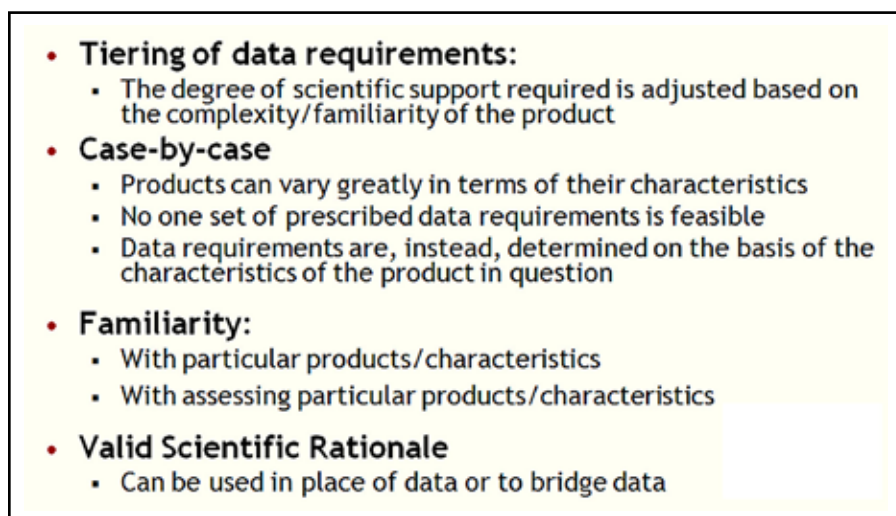
Regarding food and feed safety assessments, eight general considerations are applicable:

- A history of safe use
- Dietary exposure
- History of the organism(s)
- Characterization of the derived line in relation to the parental varieties
- Genetic modification
- Nutritional change
- Toxicology and allergenicity
- Chemical change.

More information on these factors is on our website.

ASSESSMENT PRINCIPLES

Essentially, we follow basic assessment principles (Figure 7), the first being tiering of data requirements, *i.e.* the degree of the scientific support required is adjusted based on the complexity, or our familiarity with, the product. Acknowledging that every product is unique, each has to be judged on a case-by-case basis. Products vary greatly in terms of their characteristics and no one set of prescribed data requirements is feasible. Certain



- **Tiering of data requirements:**
 - The degree of scientific support required is adjusted based on the complexity/familiarity of the product
- **Case-by-case**
 - Products can vary greatly in terms of their characteristics
 - No one set of prescribed data requirements is feasible
 - Data requirements are, instead, determined on the basis of the characteristics of the product in question
- **Familiarity:**
 - With particular products/characteristics
 - With assessing particular products/characteristics
- **Valid Scientific Rationale**
 - Can be used in place of data or to bridge data

Figure 7. Assessment principles.

considerations have to be addressed in every case, but again, each product is unique. Data requirements are determined on the basis of the characteristics of the product in question. Our familiarity with a particular product and its characteristics impacts the amount of information we require. A “valid scientific rationale” can be used in place of data or to bridge data. If it’s something that we have seen before, the proponent can present information from referee journals or the proponent’s own information to demonstrate that it’s the same as something that we’ve seen in a previous product.

A word of warning: we don’t like summary data. Companies that have submitted numerous dossiers to us sometimes include all kinds of summary data, which are not what we need. We need a rationale as to why we should look at the information we looked at with the prior product, which is much more acceptable than giving us copious summary data.

Other assessment principles are:

- The weight of evidence—the sum of the overall data submitted that provides the context for determining efficacy and safety
- Efficacy and safety side—the assessment considers the likelihood that unintended effects may be present in the modified plant in question
- Comparators must be appropriate for the product in question.

The last of these principles is included because often we receive submissions that refer to submission to the US Environmental Protection Agency, for example. When submitting for a product in Canada, relevance to Canada is preeminently important. For instance, for corn rootworm products in Canada, the corn-production system frequently includes crop rotations and other differing factors, which should be included in the story. Providing us with information on how a product is used in the US environment can complicate our assessment instead of making it easier.

DECISION MAKING AND POST AUTHORIZATION

While a file is under review, we often ask for more information to provide clarification. When all of our questions are answered, we may “flat-out” authorize a product. Or, we may authorize it with conditions, such as stewardship requirements. Some companies are now indicating to us that they never planned for a product to be marketed alone, that it would always be combined with another product. Accordingly, sometimes our conditions now reflect the fact that a product is authorized for combination with another, which affects the stewardship conditions that we will put in place. Of course, authorization may be denied. On the other hand, we’ve had files withdrawn, we’ve had files for which we have asked questions and are still waiting for answers, but CFIA has never refused an authorization.

We do not provide split—food/feed/environment—approvals. Separate decisions are posted on both the CFIA and the Health Canada websites. The applicant is required to notify CFIA and Health Canada immediately if new information on the plant becomes available, a condition always included in our authorization letter.

Compliance monitoring of conditions of authorization by the CFIA is ongoing. For instance, with *Bt* corn, resistance-management programs are in place which we actively

monitor to determine levels of compliance. Also, we work with Crop Life Canada to monitor levels of compliance from their perspective.

Stacked events constitute a special case. After a PNT has been authorized for use by the CFIA, the plant can then be traditionally bred into new varieties. However, if two or more events are combined, PBO must be notified prior to intentional release, so that we may ensure that the conditions of authorization of the individual plant lines are compatible and that a “stack” isn’t likely to create a problem. PBO must notify the proponent within 60 days of any concerns regarding unconfined environmental release of a “stack.”

IN SUMMARY

Canada’s regulations are product-based, not process-based. We have authority within the regulations for departments to approve products derived from biotechnology after the completion of the required safety reviews, and—once authorized—products of biotechnology are not treated differently from other foods, feeds or crops.

Applicants should plan for 24 months or more from submission to authorization. Ideally, less time will be required, but, especially, if we are dealing with a product type that we haven’t seen before, allowance of more time is recommended. We have biology documents that become part of our assessment, so if you know we’re going to be seeing something completely new, the more advance notice we can be given, the better.

More information may be accessed via the website URLs shown in Figure 8. For novel foods, it’s Health Canada. For novel feeds, it’s the Animal Feed Division of CFIA. Plants with novel traits is the CFIA, and there’s a CFIA Agricultural Biotechnology site for direction to various other pieces.

Talk to the regulators early and often. That’s what we’re here for and we want the process to progress as smoothly as possible for you. Again, avoid US-centric submissions.

<p><u>Novel Foods</u></p> <p>Health Canada Web address:</p> <p><u>http://www.hc-sc.gc.ca</u></p> <p>HC-Novel Foods Web address:</p> <p><u>http://www.novelfoods.gc.ca</u></p> <p><u>Novel Feeds</u></p> <p>Animal Feed Division address:</p> <p><u>http://www.inspection.gc.ca/animals/feeds/eng/1299157225486/1320536661238</u></p>	<p><u>Plants With Novel Traits</u></p> <p>CFIA Web address:</p> <p><u>http://www.inspection.gc.ca</u></p> <p>CFIA-Agricultural Biotechnology Web address:</p> <p><u>http://www.inspection.gc.ca/english/sci/biotech/biotech_e.shtml</u></p>
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Figure 8. For information concerning novel foods and plants with novel traits in Canada.



PATRICIA MCALLISTER is the acting national manager of the Plant Biosafety Office (PBO) at the Canadian Food Inspection Agency (CFIA) in Ottawa. The PBO is responsible for the confined field-trial program and the authorization for environmental release of plants with novel traits.

Ms. McAllister was born and raised on a farm in New Brunswick that produced seed potatoes, vegetable crops and beef cattle. She received her Bachelor's degree in horticulture and a Master's degree in food science from the University of Guelph. She joined Alberta Agriculture and Rural Development as a seed-potato specialist in 1997, and has been with the CFIA since 2009.

Session 3-1: The Regulatory Process and Technology Access for Specialty Crops

Q&A

MODERATOR: DAVID BALTENSPERGER

*Texas A&M University
College Station, Texas*

Alan McHughen (University of California-Riverside, Riverside). Patricia, thank you very much for your overview of the Canadian situation. I'm curious to know how many genetically engineered plants cultivated in Canada are not considered PNTs¹, and so didn't go through your approval system?

Patricia McAllister: There are none.

McHughen: Then, I'm confused about what your definition of a novel plant is. With *Bt* corn in the United States, of course we use event by event. It sounds like that's what you do in Canada as well, which would seem to be contrary to the PNT concept.

McAllister: At this point, all genetically engineered products that have been put forward have met the definition of a plant with a novel trait. The ones we have that are more unique are the ones that we regulate that the US wouldn't regulate. For instance, turf grass without question would have hit a novelty trigger in Canada. And we have sunflowers, lentils and wheat that are herbicide tolerant that were not developed through genetic engineering, and those ones are regulated in Canada as PNTs. So, we capture a broader number of products.

¹Plants with novel traits.

McHUGHEN: Right, you capture more in terms of the mutagenesis and non-recombinant things. I recognize that and appreciate that, but I also thought that the point of the plant-with-novel-trait product trigger was so that once you get an event through—a *Bt* corn, for example—the next *Bt*-corn event would not be considered novel. How do you then define the second and third and subsequent *Bt*-corn varieties as being novel?

McAllister: There is certainly a lot of talk about where it will go, but at this point each one is triggering the regulations as it comes through.

McHUGHEN: Is there something in the trait? I'm confused about that now because I thought that the system was developed in Canada so that subsequent things that don't have new traits would not be captured. What is the scientific basis for a new trait that is the trigger?

McAllister: I am unable to answer that question. I have been with this group since September and my job has mostly been issues management. A few things—like alfalfa—have created havoc for us. I was not part of the development of these regulations and I simply work with what we are given. But, believe me, our major players are frequently asking us, *When are you going to the “me too” products—when you've already looked at a trait?* They certainly can go into conventional breeding. We don't have to approve individual varieties, but, if you are modifying your event, we are still going back and looking at it again.

Julie Svetlik (Texas A&M AgriLife Research, College Station): I think Patricia already answered this question for me—thank you—so the question is for the US agencies. Assuming a plant or product has cleared the regulatory process in your agency and has been authorized and has entered the market, are there procedures in place at your agency to reevaluate status if new data come out that indicate that the plant or the product is not safe for humans or the environment?

David Heron: I'll go first since ours looks like once our hands are off, they are always off—but if new evidence demonstrates a risk as a plant pest, then we do have the authority to bring it back under the regulation. We have not seen that yet.

Robert Merker: We have seen a number of instances in which new data have been brought back to us at some point or other, but it has always been data that do not change the final conclusion of safety.

Chris Wozniak: Our statute is a bit different. FIFRA is a licensing statute, so as long as you want to distribute, sell or use that pesticide in the United States, then you are under the license, meaning you pay an annual maintenance fee, you have to supply reports on sales figures, *etc.* But you are also beholden to a clause referred to as “6(a)(2),” where, if there are any adverse effects—and that is determined by the agency not by the individual so much—anything unusual has to be reported to the agency in a timely manner and we

maintain a database of what we call “6(a)(2) events” and determine whether they require follow up. In addition to that, because it is a license, all of the registrations have a term of expiration and these will vary. For example, with the *Bt*s, part of it depends on the durability of the product. The product seen as being durable in terms of resistance to insects might get a 10- or 12-year registration. If it’s a single-trait product, it’s more likely to get a 3- or 4-year registration and, at those times, they are reassessed and they may enter what is called a re-registration or re-review process, where people basically look at the literature and look at what is known, and anything else that may have come up since the initial registration and then make a determination of whether data are required. We have a process that is called “data calling,” where, if something comes up, we can request that information.

Robert Wager (Vancouver Island University, Nanaimo): Each of you, in your own way, has mentioned that GM crops and non-GM crops with similar traits are regulated roughly the same way. My question goes to Cry proteins, and it appears to be that that’s not always the case where you have significant regulatory requirements for a GM crop with a particular Cry protein engineered into it, whereas I don’t seem to see—perhaps I’m wrong on this—any real regulations involving using the *in vivo* whole bacterium expressing the same proteins and I’d like to understand if, in fact, that is true and, if so, why?

Wozniak: If you are speaking in terms of using either a spore or spore-plus-cell prep as a biopesticide—yeah, we certainly regulate those. We have both engineered and non-engineered forms of *Bt* as well as dozens of other microbes for use as insecticides, nematocides and even some as herbicides. So I’m not sure why you are picking on *Bt*. Any microbial agent, whether it’s a virus, bacteriophage, protozoan, alga or fungus, that has a pesticidal claim associated with it—in other words preventing, destroying or repelling some disease or pest—is a pesticide under our law. I think, at last count, we have 97 active ingredients and from those stem hundreds of products.

McAllister: From the Canadian perspective, those would not be regulated by the Canadian Food Inspection Agency, but would be regulated through Health Canada’s Pest Management Regulatory Agency.

Bob Avant (Texas AgriLife Research, College Station): Recently, the USDA said they are going to go into a full blown EIS evaluation of new genetically engineered events, and I would like to hear some conversation: does that really change much about what we are doing? Is it going to delay the process? The conventional wisdom is, anytime an EIS is required it costs millions of dollars, it takes years to do and it’s a good way of delaying things. Does it represent any change or is it just another hurdle we are going to have to cross to get down the path?

Heron: As far as whether everything is going to require an EIS, no it won’t. An EIS, for those of you unfamiliar, I referred to as environmental assessments under NEPA,

the National Environmental Policy Act. If an agency cannot come to a finding of “no significant impact on the environment” when they do an environmental assessment, if they want to proceed with considering the action, then they can go to an environmental impact statement, which is a more involved process and, like the environmental assessment, has public involvement. The agency has interaction with the public throughout the process. But, the fact that these are now being open for public comment on the process called “scoping” to see the extent of the environmental impact statement, it does not mean that it is going to happen for all. These were seen as issues that are very closely related and it would be difficult to consider them separately. The decision on whether federal agencies choose environmental impact statements or environmental assessments is rather complex. It involves legal reviews with the department, interaction with the Council on Environmental Quality, which is a lighthouse that takes a look at NEPA and its obligations to federal agencies. Maybe that’s a long way of saying that no, this is not going to be the standard and yes, it is a more involved process.

Bill McCutchen (Texas AgriLife Research, College Station): A scenario here for you to think about. What would be the steps if, let’s say, a spinoff company from Texas A&M or another university were put in place for a specialty crop whereby—and I know this is a big “if”—if we had freedom to operate and we had a license for a previously approved herbicide and or *Bt* gene and we wanted to put that into onions or another vegetable, would we be required to go through the entire process again in terms of digestibility, allergenicity? Because, a big expense is the non-target organism piece—doing the types of tests that require, as you know, a lot of work and money. So, would it be possible to license from Monsanto or DuPont, let’s say a spinoff company for our university of a previously approved gene for herbicide and insect resistance and assuming we had freedom to operate for agrotransformation, *etc.*, what would be required?

Heron: We regulate organisms. We don’t regulate genes. Congress set out the definition of a plant pest, so that sets the parameters. When we are making a decision for non-regulated status it’s for the organism. It’s not for the gene. The information we may have in looking at a gene in another organism may inform our review subsequently but that would not mean that you don’t come in if you take a *Bt* or herbicide tolerance cassette and put it in onion instead of cotton. The onion would still come through us.

McCutchen: I understand that. I’ve been through this process many times in a former life, but if this has already gone through tox tests, non-target organisms, from a scientific standpoint—I understand there is law and regulation—why can’t we get together and streamline some of these things and help our producers help themselves? Can we work across agencies and with institutes to develop new products that aren’t so new but are in different vehicles if you will?

McAllister: From the Canadian perspective, if we are more familiar with things it can make it easier. It’s how you can communicate your story, but, in reality, you would need

to speak directly to our specific assessment group. If it's in a new plant, it's definitely going to be assessed as a new product, but whether you'd have to redo the allergenicity data and the other toxicity data for genes that we are very familiar with, that would require a very specific discussion.

Wozniak: Where it truly is the same gene and not some modification or a similar type gene, there is a process called "data compensation" where you can compensate the company that originally submitted supporting data. So that's one avenue. In terms of the environmental side of the equation where you are looking at non-target effects, if you are changing the exposure scenario then it is likely you are going to have to look at some data generation for specific pests. In other words, the beneficial insects you choose that might be representative of a corn field in Iowa may not be the same as that represented by an onion in Texas. So that would be up to the risk assessor to determine what types of studies would have to be generated *de novo* and which ones could be bridged. We do occasionally bridge data, particularly so with microbial agents, but certainly it's plausible with some of the PIPs. Now, as for the larger question in getting away from event by event transformation even within the same species, you can take a PIP that's been registered in field corn and do the appropriate crosses, you know, typical sexual, traditional breeding crosses, move it into popcorn, and you are covered as far as the tolerance goes and all that. However, one of the arguments that has been made—and I'm not saying I agree with it 100 per cent—but if you generate a new event through transgenesis, either through *Agrobacterium* or the gene gun or whatever your mechanism, then your position within the genome, as far as where your transgene inserts, can influence the pattern of gene expression. So, in our case, one of the things that we look at relative to non-target effects but also just for the overall accumulation of your pesticidal substance, which needs to be recorded on a confidential statement, that requires an assessment. You know, is it identical just because you used the same promoter and the same open reading frame and the same termination sequence if it's in two different crops or even within the same crop but it's in two different positions? That's the crux of the argument. At what point do you say, *Well, we've seen this enough and the likelihood of that happening is small enough*, I think that, in some respects, is what we are moving toward, but as far as going between different species, like, say, onion and corn, that's a larger question.

Merker: I defer to EPA on pesticide issues, but, for food and feed safety, if we've seen the proteins before, essentially we've seen the proteins before. The allergenicity assessment and the assessment for toxicity would be the same and could be done either by incorporation by reference or by summarizing what information we had seen before and where we could find it. Certainly we wouldn't make somebody do that over again, and, as a for instance, if you were dealing with our favorite antibiotic resistance marker, NPTII, we actually approved that as a food additive, and even if you were using it in one of the crops for which it wasn't approved, if you pointed us to that approval, certainly we would want to know the specifics of how it got integrated, but the safety of the protein could be referred back to our regulation.

Wozniak: One thing I want to clarify—just to make sure—there is a difference between what's ruled under FFDCA like the tolerance action, versus what's under FIFRA, which would cover, for example, non-target effects but also human health effects. So, for example, if you are working with Cry1Ac as your insecticidal protein and it's already covered by a tolerance, then you don't have to redo the studies that are associated with that tolerance. It could be an oral tox test, allergenicity, *etc.* However, on the FIFRA side, if the concern is more about exposure of non-targets then that is where the data compensation would come in—where you would likely pay another company to utilize their previously submitted and accepted data.

Charles Rinerson (Texas AgriLife Research, College Station): Dr. Merker, the basis for the consultation and regulation you were talking about earlier was based on the FD&C Act. Do you see a different consultation process or considerations if the plant or product were regulated under the DSHEA Act²?

Merker: Certainly, if it comes in for something in a dietary supplement, and there has been a history of exactly one of those coming in. It may fit the criteria for consideration as a new dietary ingredient and it would be the substance going into the dietary supplement that would need to be looked at, not necessarily the whole crop.

Roger Beachy (Global Institute for Food Security, Saskatoon): I'd like to take us back just a bit—and maybe this is too big a question to answer today—but, in 1987, when the coordinated framework was developed, it was expected that there would be a full reexamination of the coordinated framework in some period of time, 7 to 10 years, and that we would learn from those 7 to 10 years about what to go forward with. In fact, some of the original challenges were to try to eliminate regulations based on what we'd learned in the first 10 years. We haven't done that yet. We've learned more about what to regulate, what we think we know about to regulate, but in fact, regulation is not simplified, it's made more difficult because we keep adding more on each time someone raises a possibility of potential damage or danger. When is it time to re-evaluate the coordinated framework and come up with a new framework? We are now more than 20 years in and we haven't re-evaluated. When is it time to take the learnings of science since 1987 and redo the coordinated framework based upon what we've learned and what we expect to see in the following two or three decades? I ask the question because most of us feel that, given what happened in 1987—and I was involved in that process too—but Nina Fedoroff and others have reminded us that this is the way that we would start, but we expected to deregulate it more fully and make it easier to innovate, and it's not. I do appreciate the learnings and the ability to cross back and go back to old data and restate them. It should help Texas A&M to simplify, but it's still a more expansive program than had been imagined in 1987. Can you help me understand where we might be in 5 or 10 more years?

²Dietary Supplement Health and Education Act.

Merker: I don't think—from FDA's point of view—that it really has changed. I actually think that our 1992 policy is pretty flexible. Certainly, it's a situation where if the developer wants to seek us out they can and we are available. And the issues are going to be the same: safety and nutrition. As long as those get covered we are happy to consider things. We actually didn't think we would be doing this for this long, but the developers seem to want it, I think mainly for international trade issues, and the public seems to want it as well.

Heron: Yeah, that's an interesting point because, actually in 1992, OSTP³ put out a second document that was actually calling for what you are saying here Roger, to dial it back wherever possible. What I have seen is that unless there is a sustained push in a certain direction it doesn't happen, so the *status quo* stays in place. And so, at the regulatory agencies, we try to run the mousetrap as best we can whether the mousetrap itself has a faulty design, that has to come from outside. I mean, this administration with the Holdren memo, has restated the principles of the Reagan administration. But, in terms of what it actually means in practice—and this is where the distinction between what is in the law and what is placed in regulation and how that works—you can see now that this whole premise of presumed innocence of things developed through genetic engineering has been turned on its head, and so now we are trying to prove a lack of harm, which we all know is impossible to do.

Wozniak: Certainly, I understand your frustration with the lack of change. I think Dave Heron makes an excellent point though, in that it is the actual practice of what is performed, in terms of regulation or deregulation or consultation, depending on the agency. But, in terms of the coordinated framework, I don't think it's a bad idea to reassess that. One of the decisions that was made was to use existing statutes to cover the bases and I'm not going to voice an opinion one way or the other on whether that was a smart idea, but what I will say is that some of the changes that you are talking about require legislative action and have to be done on Capitol Hill, not at EPA or APHIS or FDA, unfortunately. And I think that's part of the frustration, but, again, Dave's point: those changes require forward-thinking people who aren't afraid to take some risk and perhaps some backlash from the public in terms of making some bold moves. Now, one of the things that we have heard about—and it's very obvious to everyone in this room—the lawsuits, for example, that APHIS has had to endure over these last years are always part of the battle. If you try to be progressive and say, *Well, we've seen this enough we don't really need to regulate this*, there are going to be a whole bunch of people on the other side who say, *Oh yes you do*. The Federal Register notices get 50,000 to 60,000 comments, *etc.* But I think you are right that it certainly is time to move forward and use some of the familiarity we have with these products such that, even if we do regulate them, we do it a much reduced level—basically you would be more cataloging them than regulating them. Again, it's going to take somebody with a bold heart who is willing to take a beat-

³Office of Science and Technology Policy.

ing to move that forward. Certainly, there is still the issue—although I don't think it's an insurmountable one—where I talk with a lot of foreign governments and it makes them very nervous to think that we're going to have certain things that aren't really scrutinized properly, but some of the companies also tell me, *Don't worry about that. We'll deal with those individual countries in terms of trade. We'll work around whatever their requirements are.* I want to mention one of the proposals we are considering, or reconsidering, and that is a cisgenic exemption with cisgenics defined a little bit more broadly than perhaps is done in the literature. We are in the early stages of reviving that, which is part of a previous data-requirements rule that never got off the ground a few years back. So, that's one instance where, I think, philosophically, it's a major move for the agency to consider a product of recombinant DNA that doesn't require regulation. It's not going to solve the problem for everybody for sure. Those people who still rely on basic transgenesis with foreign genes—it's not going to help them one iota, except in terms of moving that ball forward and saying, *Here's something where we don't have to be concerned just because it's genetically engineered.*

**Session 3-2: The Regulatory Process
and Technology Access for Specialty Crops
(continued)**

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Getting to Yes: How to Achieve Pre-Market Approval

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Thenell & Associates is a regulatory consultancy that provides expert advice and support to companies that make and market genetically engineered plants for food, fiber or fuel. We help clients plan and execute product approval strategies and support their R&D programs from discovery through commercialization. Our clients include start-ups, early and late-stage product developers, mature multi-nationals, and universities. With more than 20 years of practical experience working with US federal and state regulators, we've helped two dozen companies advance their commercialization goals.

We also do some biopesticide and biofertilizer work, and have also done work with genetically engineered microorganisms for industrial purposes. In 2006, together with three colleagues in the United States and Europe, I co-founded the Agricultural BioTech Regulatory Network. The ABTR Network is a group of regulatory professionals serving the agricultural biotechnology industry from product concept through commercialization. It's a network of well qualified regulatory experts who specialize in genetically engineered plants and plant products. Today, we have members and affiliates on four continents serving major ag-biotech markets (Figure 1). Through the ABTR Network, we are able to offer clients global understanding and support typically found only in multi-national companies. We need to be able to offer this perspective because what is cultivated here in the United States doesn't necessarily remain here in the United States.

SPECIALTY CROPS: PREMARKET APPROVAL

It is not uncommon for scientist who have deployed genetically engineered traits in specialty crops to fail to initiate the process of obtaining premarket approval, or—having initiated the process—have failed to complete it. Commonly heard reasons for cessation, from university research directors, include:

- “It’s not the objective of our research. We are here to do the proof-of-concept, the discovery, to fulfill the obligations of our grant without the intent to commercialize. We publish papers and then move on to the next grant.”
- “We don’t know where to start.”
- “It’s too complicated.”
- “It’s too expensive.”
- “There are intellectual property constraints.”
- “We have concerns over product liability and stewardship—potential for lawsuits.”
- “Without a commercial partnership, there is no obvious outlet for the discovery.”
- “No mechanism exists within my university to commercialize.”

Taken together, these are daunting impediments. On the other hand, with good planning, the regulatory issues are not overly complicated. I will describe some of the lessons I’ve learned from working in ag-biotech regulations since 1990 in hopes that it will de-mystify the product-development process and demonstrate that pre-market approval for genetic traits produced by public-sector researchers is possible. My intention is not to make you an expert, but to convince you to hire the best help you can afford when you need it.

WHERE WE ARE AND HOW WE GOT HERE

By some measures, biotechnology has been remarkably successful. Since commercial deployment in 1996, global acreage has increased at double-digit rates for 17 years. It has been claimed that agricultural production has increased by nearly \$100 billion in that time. Myriad environmental benefits have accrued from changes in weed and insect control measures, from conservation tillage, from reduced mycotoxins, *etc.*

Data published by the International Service for the Acquisition of Agri-biotech Applications (ISAAA) indicate that 28 countries have approved some 325 unique crop/trait combinations to date (Figure 2). And although specialty products were the very first approvals, the vast majority of today’s production is limited to variants of two genetic traits in commodity crops. Specific numbers are hard to come by, but I submit that specialty crops account for less than one-tenth of one percent of the 420 million acres of GM crops produced in the world today.

The power of this technology isn’t finding its way to green grocers’ shops and produce aisles; the regulatory environment is often cited as one reason for the dichotomy between agronomic and specialty crops. With divergent regulatory requirements around the world, premarket approvals have to be acquired country-by-country. Only certain countries have regulatory systems in place, and only some of these have functional systems. Furthermore,



Figure 1. Agricultural BioTech Regulatory Network.

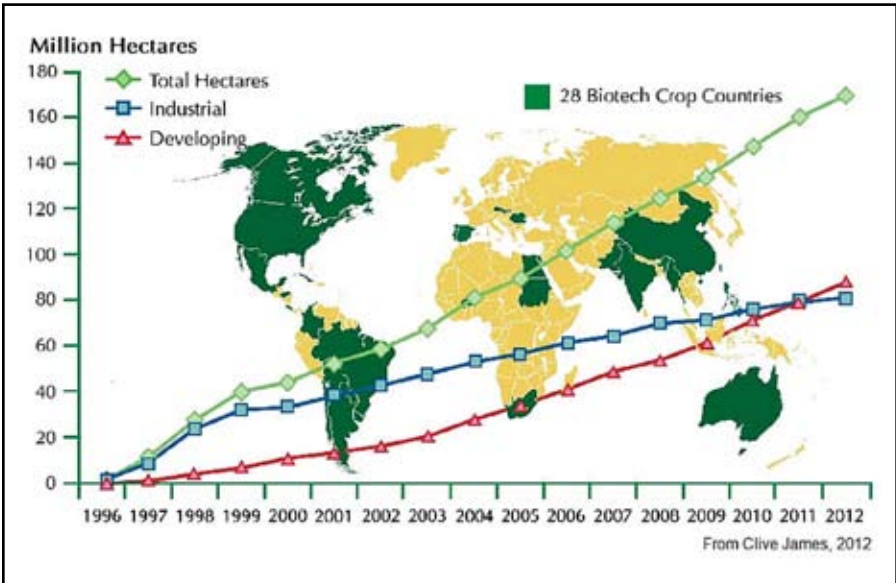


Figure 2. Global GM-crop status.

pre- and post-market requirements vary considerably. Global registration is necessary because, as said before, many of these crops move in international trade. Specialty crops are not necessarily an exception. In the tomato industry, for example, fresh-market produce is the primary outlet, but, additionally, tomatoes go into processing. Similar crops

have components that become ingredients of foods that move in international trade, and issues come up needing regulatory approvals in other countries. Also, only certain countries have functional regulatory systems and certain countries have higher impediments to commercialization than does the United States. Internationally, regulations are not harmonized although there are some reasonably harmonized regulatory risk-assessment criteria. The net effect of this is that when amortized over the thousands of acres of specialty-crop deployment versus the millions of acres in agronomic crops, certain of the regulatory costs make it prohibitive to deploy technology in specialty crops. For this and various other reasons, specialty crops lag behind. I would like to help change that.

Other global instruments have to be considered (Figure 3). The Cartagena Protocol established minimal requirements on trans-boundary movement and use of living modified organisms. It's particularly important in less-developed countries that don't have national legislation governing genetically engineered organisms. Established in 2003, it's based on the precautionary principle, and it has some additional issues concerning advanced informed consent before one initiates trans-boundary movement, as well as liability and redress provisions for environmental contamination that are still being worked out. As of 2013, the Cartagena Protocol has been adopted by 165 countries. But the United States, Australia and Canada are not signatories. Risk-analysis principles—pertaining to genetically engineered food—were promulgated under *Codex Alimentarius* also in 2003; they are internationally recognized as meeting WTO commitments. Those principles are generally consistent with US safety standards and with the Biosafety Protocol. In addition to the WTO agreements, a number of bilateral agreements are in place to facilitate trade including trade in genetically engineered foods and feeds. The WTO agreements have been invoked in trade disputes between members with varying success.

Upcoming negotiations between the United States and Europe will probably include genetically engineered foods.

US COORDINATED FRAMEWORK

In the United States, we operate under the Coordinated Framework for Regulation of Biotechnology Products. Three federal agencies share primary responsibility for assuring safety of genetically engineered plants and plant products, in accordance with their respective legal authorities:

- USDA-APHIS (US Department of Agriculture-Animal and Plant Health Inspection Service)—safety of genetically engineered organisms in agriculture and the natural environment,
- FDA (Food and Drug Administration)—safety of foods from genetically engineered organisms used for food and feed,
- EPA (Environmental Protection Agency)—safety of pesticidal substances produced in genetically engineered plants or microbes.

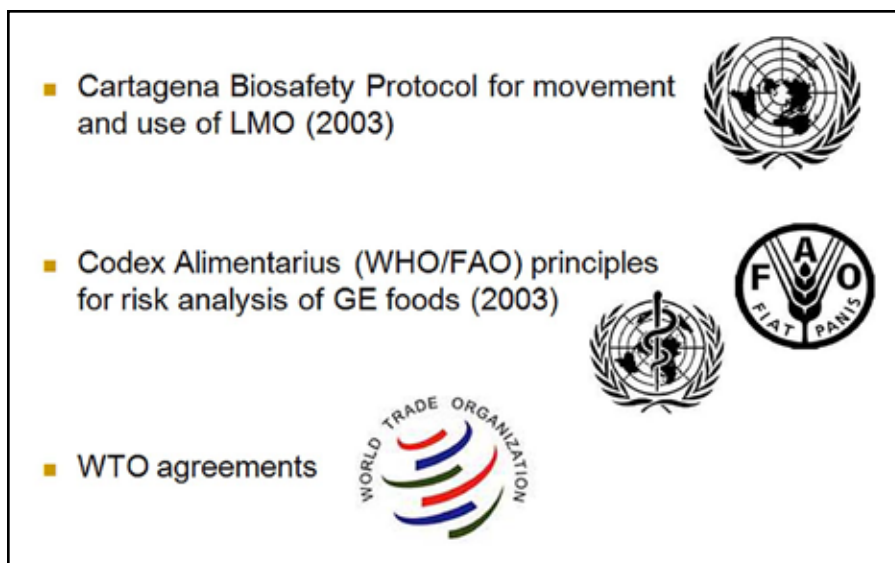


Figure 3. Other global instruments.

USDA-APHIS¹ is the agency likely to be encountered initially when developing and deploying a genetically engineered plant product, in terms of environmental safety, field testing, and/or interstate movement. Bob Merker² with FDA mentioned early food-safety assessment for novel proteins that are introduced in field testing so that, should there be any adventitious presence, the food/feed safety concerns would already have been addressed, at least at a preliminary level. And Chris Wozniak³ with EPA talked about the safety of biopesticides and plant incorporated protectants. This comprehensive—if somewhat complicated—system has worked fairly well since the mid-1980s, although it may be argued that improvements are now needed.

CONTINUING CONTROVERSIES

However, even after two decades of commercial use, many recent headlines have focused on controversies around the deployment of genetically engineered plants (Figure 4). Litigations over stewardship lapses and disrupted trade have cost technology providers hundreds of millions of dollars, with lawsuits over intellectual property rights and over government approvals, some of which have made their way to the Supreme Court. As a result, approval times for genetically engineered crops have ballooned from approximately 6 months to over 3 years. Happily, in 2011, USDA implemented process improvements to reduce approval times considerably.

¹Pages 141–148.

²Pages 151–160.

³Pages 131–139.



Figure 4. Recent headlines.

LABELING

Controversy continues around labeling. In 2012, Californians failed to approve a labeling initiative at the ballot box, and, more recently, the Senate struck down a labeling amendment in their version of the Farm Bill. Some people remain deeply passionate about the need for labeling of foods with genetically engineered ingredients although no health or safety reason justifies it. The advocacy group, Center for Food Safety, claims that 25 states have introduced bills to require labeling or restrict genetically engineered foods.

All of these issues play some role in the decision to deploy a genetically engineered trait in specialty crops or not.

PRODUCT DEVELOPMENT

Despite all of the challenges, genetic engineering still holds tremendous potential for improving agricultural yields in the face of continuing challenges from pests and disease, climate change, and population growth. So the question is: *How does one deploy this technology and bring a genetically engineered product to market?* The process involves multiple disciplines working to address various interests that are, oftentimes, not well aligned (Figure 5). The regulatory piece is just one discipline, the purpose of which is to meet all domestic and international approval requirements premarket in those countries wherever one intends to cultivate, to export, or to otherwise market the plant product. The challenge, of course, is to coordinate these efforts to achieve timely completion and enable product introduction to the greatest extent possible. Fulfilling regulatory requirements is often critical to success.

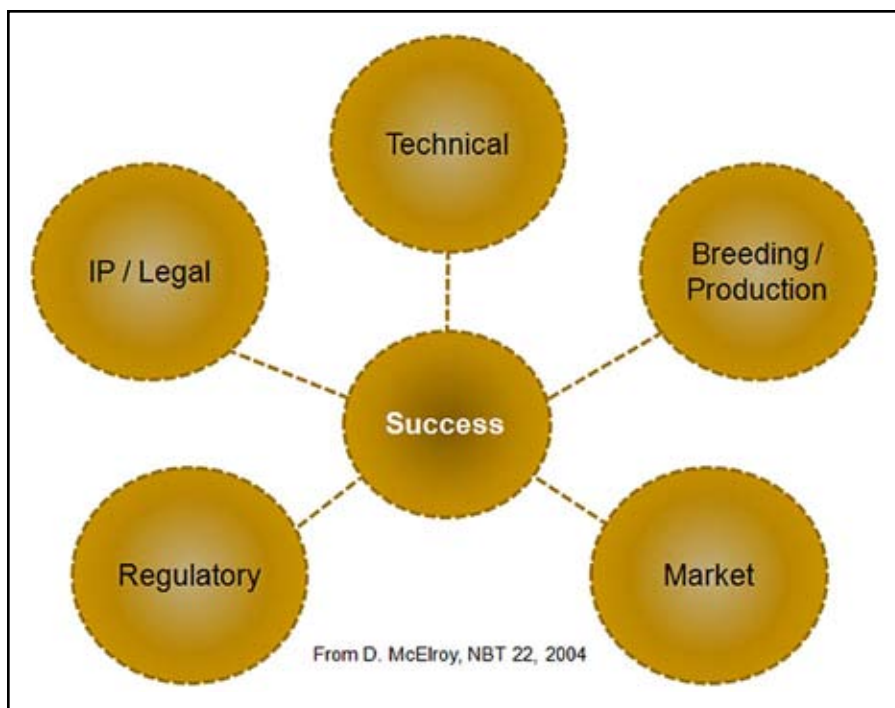


Figure 5. Product development–1.

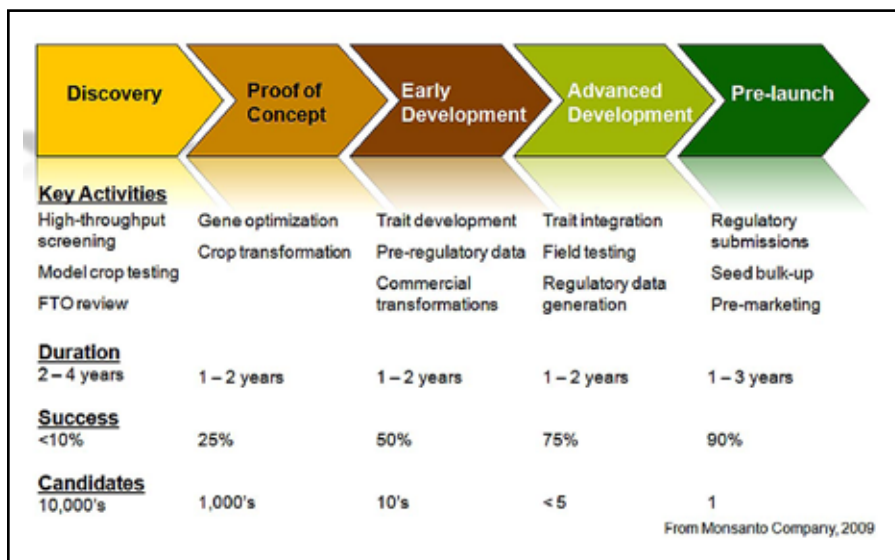


Figure 6. Product development–2.

In the product-development scheme, the major technology providers have adopted some type of systematic approach to creating new crop traits (Figure 6). The process can be organized in stages with defined criteria that must be achieved before advancing to the next stage. By adopting a system of “stages and gateways,” the process is more disciplined, thereby helping management of risks and costs at each stage. It can transit from a gene-discovery phase through proof-of-concept, often in a model crop and ultimately in the crop of interest. It moves into an early-development phase in which the trait and its utility are validated, generating pre-regulatory data for the crop intended for market. It advances to trait integration in other germplasm, with field testing to generate regulatory data, and, finally, into prelaunch activities, bulking up seed, and premarketing activities. Duration can vary. Success rate increases in accordance with decisions around event selection, and the number of transformants—the number of candidate lines—decreases until, at the end of the process, focus should be on one, maybe two, commercial events. By adopting this “stages and gateways” approach the process is more disciplined, and it helps manage costs and the risks at each stage.

REGULATORY ACTIVITIES

Each development stage has characteristic regulatory activities and defined criteria for passage to the next stage (Figure 7). The earliest stages involve preliminary analyses of the crop biology and the product concept, and looking at some issues that might occur with deployment of a particular trait in a particular crop species. At proof-of-concept, early work comprises evaluation of whether the active molecule or the technical effect has some human health or safety or environmental safety issue; also analytical tools and reagents are being developed, and protein production and characterization, particularly if additional animal testing is needed, for example. The early stages involve generating protein-safety data on the introduced traits—so-called “core-package” data—and supporting field evaluations and testing. In the later stages, the heavy lifting begins from the regulatory point of view: a number of studies are needed to characterize and create safety data on the lead commercial transformation event—so-called “event package” data—assembling the registration dossiers and managing their submissions. Critically important decisions must be made before entering this phase, as the costs of generating data increase dramatically and the cost of failure at this stage can be high. Molecular characterization is involved as are compositional analyses, agronomic studies, effects on non-target organisms, animal-performance studies, and determinations of environmental fate and toxicology. Finally, at the prelaunch stage, dossiers are compiled and regulatory submissions are managed through to completion.

Much has been said about the high cost of achieving regulatory approval for genetically engineered crop traits. Published numbers range from \$6 million to \$15 million for global approval. A recent study quoted \$35 million for global approval. Although these costs are real, they are inflated inasmuch as they reflect the fully loaded costs of supporting expensive infrastructures to support global deployment. In fact, regulatory approval can be obtained for considerably less—at least in order of magnitude less.

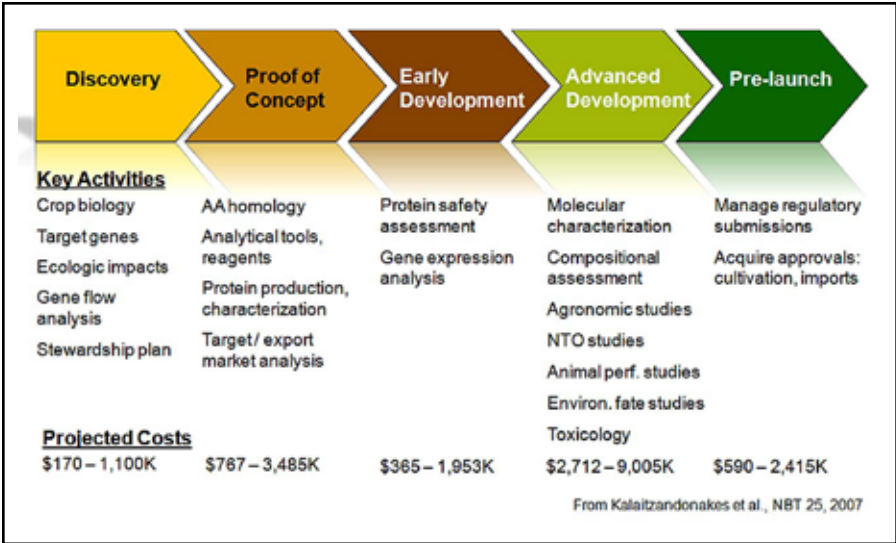


Figure 7. Regulatory activities.

PRODUCT DESIGN

Early in their deployment, novelty seemed to drive introductions of genetically engineered foods. However, it soon became clear that market pull trumps technology push. So when asking whether to move forward with the genetically engineered specialty crop, critical questions are:

- Why this?
- Why here?
- Why now?"

The market needs to be assessed efficiently and effectively. It is vitally important to “map” stakeholders to gauge market acceptance and vulnerabilities. Products can achieve technical success, but fail in the market because of lack of acceptance somewhere in the value chain; it can be an expensive lesson.

Regulatory guidance in product design is important (Figure 8). There are myriad places to stumble, but they are largely avoidable *vis-à-vis* regulatory activities. With expert and timely guidance, significant savings are possible in the cost of a regulatory dossier while maximizing the chance of timely approval. On the other hand, I have seen examples of products designed without regulatory input, mainly proof-of-concept projects: “We threw some genes in the plant, we got a great phenotype, so let’s make it a commercial product.” This can cause significant regulatory heartburn due to poor construct design choices or incomplete information. Seeking out regulatory guidance in the early stages is likely to

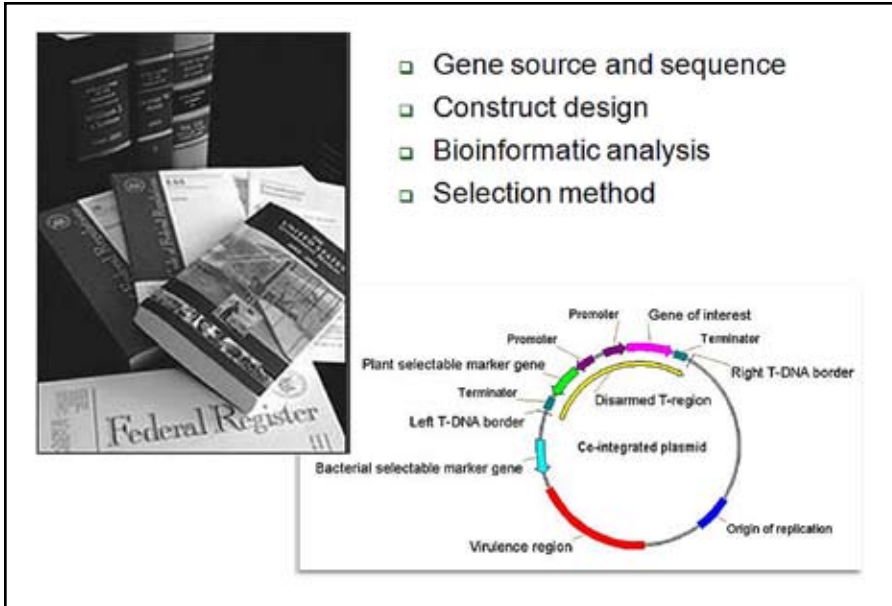


Figure 8. Regulatory guidance in product design.

be a good investment. Strategic and practical regulatory decisions should be considered in product design (Figure 8), including:

- New breeding techniques like precision genome editing can lead to products that are outside the scope of certain regulations and their associated compliance costs.
- For other genetic modifications, early regulatory input on the source of genetic elements, construct design, transformation and selection methods can reduce regulatory data costs later on.
- Conducting a detailed regulatory assessment, at the product-concept or the proof-of-concept phase of product development, is highly recommended.

A good-quality assessment by a consultant will identify the prospective data set, the costs involved, and the timeline to be expected. Once you've "pressure" tested your product design with an expert, it's a good time to consult with your regulatory authorities.

Representatives of USDA-APHIS, FDA and EPA are an excellent resource, and each federal agency has a mechanism by which a developer can meet to discuss their project development. The purpose of such meetings is largely to confirm the regulatory strategy and inform the regulator(s) of the project. It is also an opportunity to confirm the scope of data necessary for pre-market approval before commitment to expensive studies. Depending on how novel is the crop trait or technique is to the particular agency, there should be several consultations during the course of product development (Figure 9).

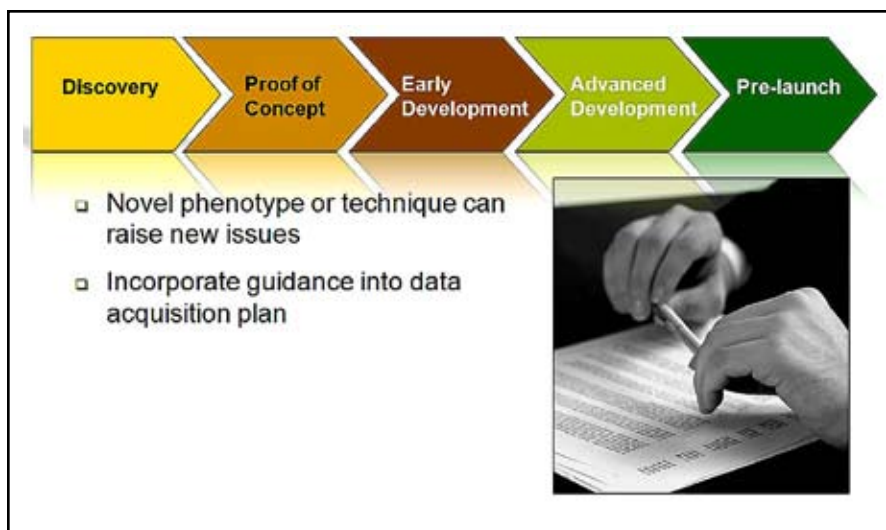


Figure 9. Consultation with regulators.

ANALYTICAL TOOLS

Analytical tools and reagents are a vital part of preparing the “core-package” data for pre-market approval. Consultation with regulators is particularly important if novel methods have to be developed, to produce the right kind and quality of safety data. One also needs to make sure that these methods are validated in the matrix that you’re using, and under actual conditions. Good laboratory practices (GLPs) can be expensive. At a minimum, work by contract labs should be conducted with GLPs, including analytical chemistry, animal testing, compositional studies and nutrient analyses. Whether field work is hired out or is performed within an intramural non-GLP research program, it is vitally important to maintain careful records for regulatory compliance.

At each developmental stage, the transformation events created must be screened for various characteristics and only those meeting specifications selected so that they will eventually gain regulatory approval. Approval can be delayed or even derailed because they have not had the appropriate selection.

For regulators, transparency is particularly important. They like to see peer-reviewed literature describing performance and safety of a new trait. It contributes to their familiarity, and it can make their decision making appear not solely based on proprietary company data. Accordingly, publishing results of efficacy and other testing is recommended.

STEWARDSHIP

Good stewardship—vital to obtaining pre-market approval of genetically engineered crops—may be thought of internal quality-assurance procedures. Stewardship practices are largely, in my view, internal quality assurance procedures applied at each stage of

development to ensure product integrity throughout the lifecycle. It's important to maintain unique identifiers and meticulous records to ensure that the commercial product is nothing more or less than it is intended to be. Although good stewardship practices cannot eliminate human error or natural phenomena, they go a long way to minimizing events that lead to "front page news"; shortcutting can be costly.

IN SUMMARY

The challenges involved in bringing a new genetically engineered crop trait to market can be daunting. There are many possibilities for things to go terribly wrong. Regulatory expertise will not necessarily solve all of the impediments to achieving market success. On the other hand, with careful planning, regulatory approval doesn't have to be an insurmountable impediment.



SCOTT THENELL is founder and managing partner of Thenell & Associates LLC, offering expert regulatory advice to companies that make and market genetically engineered plant products.

His career spans more than 30 years in technical and regulatory service to the food-processing and biotechnology-seed industries. Since 2001, he has helped clients reach their regulatory goals for biotechnology-derived food and energy crops, industrial products, biopesticides and soil additives. He is a co-founder of the Agricultural BioTech Regulatory Network, an international group of independent regulatory professionals serving the agricultural biotechnology industry from product concept to commercialization.

Mr. Thenell earned degrees in bacteriology from the University of Wisconsin-Madison and in regulatory science from the University of Southern California School of Pharmacy.

Cultural Shift: Innovation is a Process

PETER SCHUERMAN

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Presentations at this conference demonstrate that the commercialization of genetically engineered traits in specialty crops is a complicated process. Furthermore, university researchers are more accustomed to thinking about innovation as an event rather than as a process. Within Texas A&M AgriLife Research we are taking on the challenge of how to look at innovation as a process and how to steward innovation beyond simply publishing, to create opportunities for our industry partners. In so doing, we are addressing a fundamental problem: the weakness of the pipeline.

UNIVERSITY CULTURE

We are not trying to change the university, but rather to change the boundaries of what it can do, because university culture is vital and important for society. For us, innovation is about exporting something—our product. Every transaction with the world is about innovation. Resources come in; innovations go out. Although research is not a simple matter, conceptually it's simple. Conducting research is complex. When research results are generated, they are interpreted and captured in a form that can be communicated as a channel to the marketplace. Principal investigators are a type of entrepreneur in that they convert resources from their stakeholders, federal and state agencies for the most part, and turn them into products: publications, which create professional success. It's a well understood process.

CORPORATE CULTURE

For corporations, innovation is about a product or a service. Regarding plant-biotechnology traits, the method of production is far more complex than just research. Even when a new trait has been evaluated and deregulated—having gone through the regulatory approvals process—it still has to have a channel to the marketplace which involves having freedom to operate, involving patenting, and thorough understanding of the marketplace. It's a dynamic process.

THE CONTRAST

Contrasting the two, one has a fairly quick turnaround whereas the other is like a slog through mud. The challenge for universities is to figure out how to be part of this whole process. Dennis Gonsalves¹ talked about his work in terms of a public-sector anomaly. I give him a great deal of credit for having the fortitude to take on that task. A lot of researchers, not just those developing in plant biotech traits, are unwilling to face the challenges involved in commercialization. Publishing papers is a much more immediate fix. There's nothing wrong with publishing, but if we are to work in plant biotechnology, we should be ready to take on the challenge of being good stewards to the point of translating valuable opportunities to industry partners.

UNIVERSITIES: THINKING DIFFERENTLY

You cannot bring damaged goods to the game with industry. If a research result has been published, the ability to obtain patents is damaged, affecting the investment opportunity. The high cost of investment to obtain deregulation has been discussed by other speakers. Scott Thenell² mentioned that the expense may be reduced by an order of magnitude; nevertheless, a lot of money would still be involved.

Criticisms leveled by the public and NGOs against genetically engineered crops include:

- Big chemical companies are marketing these for profit.
- They are not in the best interests of consumers.

Big chemical companies *are* involved in these projects, because commercialization requires commitment and significant investment over a long period of time. On the other hand, if we can stand behind the traits that we're developing, there's an opportunity to build university/industry trust.

Why should universities be involved in this beyond publishing research papers? In 1980 the world changed as a result of the Bayh-Dole Act (BDA), which permits a university/small business/non-profit institution to use federal research funding to pursue ownership of an invention; prior to the BDA, federal funding obligated inventors to assign inventions to the government. Universities responded by forming offices for intellectual property

¹Pages 37–46.

²Pages 183–194.

management and technology transfer, which resulted in the formation of Association of University Technology Managers (AUTM), the first incarnation of which was the Society of University Patent Administrators (SUPA). At the time, they believed the important thing was to file patents, and this thinking set the stage. As a result, we now see universities carrying huge portfolios of unlicensed IP because patenting is the priority.

This is still a new process for universities, but it is endorsed by Texas A&M, which has the following mission statement:

*To provide education, conduct research, **commercialize technology**, offer training, and deliver services for the people of Texas and beyond through its universities, state agencies and health science center.*

The mission statement clarifies the importance of commercialization of technology, which is a consideration toward tenure in the Texas A&M University system.

WORKING ASSUMPTIONS

We have the legacy of viewing innovation as a researcher-initiated and -driven event. Now the “eureka” moment is viewed as justification for commercialization. Often, the first thing that the researcher does, to ensure compliance with federal laws, is to go to the website and start filling out a form to disclose the invention. The next order of business is to file a patent and license it to someone and obtain a “commercialization” notch in the belt. This eventuality may not happen very often, but it’s a common framework, a baseline expectation; it is what the BDA says should happen.

THE REALITY

On the other hand, this doesn’t fit well for biotech traits, because nowhere in this process have patenting and partnering strategies been developed. Universities do not typically engage in freedom-to-operate analyses, which is something that companies often have to deal with. Certainly, university researchers don’t think about freedom to operate when they are putting together gene constructs. We may receive an invention disclosure on a new trait composed of pieces and parts from six other collaborators, provided under individual material transfer agreements (MTAs) that preclude commercialization; complex conversations may be needed if the invention is to see the light of day. We have a distressed asset at that point, which is, unfortunately, not uncommon across universities.

A problem here is that universities are places for researchers who have decided that—for whatever reason—they don’t want to work in industry. Traditionally, professors have run self-directed programs of research within the support structure that the university provides. But, this is changing. Now we expect researchers to not only be experts in their fields, but also to be educated in commercialization and partnering with industry, which is unfair. My hat is off to productive scientists who have had the fortitude to negotiate the process of gaining regulatory approval.

Many times, I have been approached by scientists with new, useful transgenic plants that they now wish to patent and on which they initially published data a couple of years before. In contrast, the people in the university patent office are less interested in

immediate usefulness than in whether the invention is novel and non-obvious, in which case they would have patented the invention two years before. Different ways of thinking are involved due to how researchers are schooled.

On the subject of schooling, it is a false premise that researchers simply need more education on intellectual property. The concept of a talent agent is relevant: artists, authors and athletes all have agents. In contrast, researchers don't have agents; they are on their own. Historically, scientists haven't needed agents, whereas they now have to face the challenges of getting transgenics deregulated and marketing related technologies. Strategies are needed to ensure that assets are not damaged inadvertently through actions that may seem very reasonable from a research perspective. They should not be expected to be skilled in all subjects.

CULTURE SHIFTING

Managing innovation is not just about filing an invention disclosure, getting a patent and licensing it. One of the things that people often don't appreciate is that, at a very early stage, a new innovation is not separable from the innovator. Therefore, if a researcher is not interested in innovation, there should be no negative consequence. The university should still allow the advancement of knowledge through publication. Professors should not be dictated to, should not feel forced to do something they are not comfortable with.

On the other hand, that comfort zone should not be overemphasized. Scientists should be encouraged to look for opportunities to transfer their research vision into results that may change the world. An important element of that change is leadership. Those in leadership positions should not be saying, "Commercialization is not that important. Working with industry is not that important." Within the Texas A&M University system, high-level leadership espouses the philosophy that commercialization is important.

Although it is clear that researchers need assistance, sometimes they are unaware of that need. Also, deeds speak louder than words; it is important for us not to just philosophize, but actually show results. In 2006, what was then the Texas Agricultural Experiment Station—now Texas A&M AgriLife Research—hired Bill McCutchen, who not only had industry experience but also had a track record as an innovator and as a researcher (Figure 1). He was exactly what Texas A&M AgriLife needed to be able to effect the culture change.

Shortly after joining AgriLife, Bill hired Bob Avant (Figure 2) to head up the bioenergy effort, which is a pilot program to explore the concept of working with industry in different ways. It has been enormously successful, and has matured such that we now have a corporate relations program. Bob has assembled a team who now work with industry as project managers and who act as intermediaries between our industry partners and our scientists who focus on research, and so we have project managers who mediate deliverables and assist in communication, because sometimes some translation is necessary.

In 2007, I joined as the Director of Innovation Management and transformed the Office of Technology Commercialization as a liaison with Texas A&M AgriLife Research (Figure 3). I came from UC Berkeley where I'd had the opportunity to form the Industry Alliances Office, which tripled industry support for Berkeley in the first year. The simplest

Bill McCutchen, Executive Associate Director for Texas A&M AgriLife Research

- Strategic leader for trait and chemistry R&D for the DuPont Ag & Nutrition Platform
- Accrued over 55 granted patents and over 200 pending or published patent applications as a bench scientist, technical leader and coordinator of R&D initiatives
- Recipient of DuPont's and Pioneer's most prestigious agricultural R&D team award, The 2007 Henry A. Wallace Agricultural Revolution Impact Award
- Recipient of DuPont's Global Innovation and Team Accomplishment Awards and Pioneer's Inventors of the Year Award

Figure 1. Leadership in innovation–Bill McCutchen.

Bob Avant, Director of Corporate Relations & Bioenergy Program

- Former Executive Director of a State agency responsible for funding food and fibers research
- Registered Professional Engineer (Agricultural Engineering)
- 38 years of experience in agricultural and engineering systems management
- Directs major corporate sponsored research programs with a team of project managers

Figure 2. Strategic hire–Bob Avant.

way to describe what innovation management is at a university is to say that it's the same as business development anywhere else. We have created three integrated teams:

- Innovation Management
 - They help researchers recognize opportunities and advance those opportunities through strategic planning.

Peter Schuerman, Director of Innovation Management

- Founded UC Berkeley's Industry Alliances Office
- Transformed the Office of Technology Commercialization's operations in licensing and IP management and its relationship with AgriLife
- New role as Director of Innovation Management
- Works with Corporate Relations, individual researchers, industry partners and entrepreneurs to develop strategy and make deals

Figure 3. Strategic hire—Peter Schuerman.

- Corporate Relations
 - They foster strategic partnering so that, instead of thinking about the relationship between industry and academia as just a way of outsourcing some research tasks, they create audacious collaborative projects to make exciting things happen.
- Technology Commercialization
 - Protecting intellectual property and assisting licensing, understanding that they need to focus; every time we say “yes” to something that isn’t any good, we are saying no to something that is. By setting priorities, they are masters at creating win-win arrangements with our industry partners.

VALUE GENERATION

From 2003 to 2007, things were pretty flat, but the creation of resources and infrastructure within Texas A&M AgriLife has met with success since then (Figure 4). The bar graph shows engagement from outside. The line graph shows engagement from inside.

There is opportunity for continued improvement; we’re still innovating in how we manage innovation, but we think that we are on the right track with an infrastructure that supports researchers. The first questions we have for them are:

- “What is it you’re trying to do?”
- “What is your vision?”
- “How are you trying to change the world?”

And we are asking our industry partners:

- What is it that’s keeping you up at night?
- What are you trying to achieve?

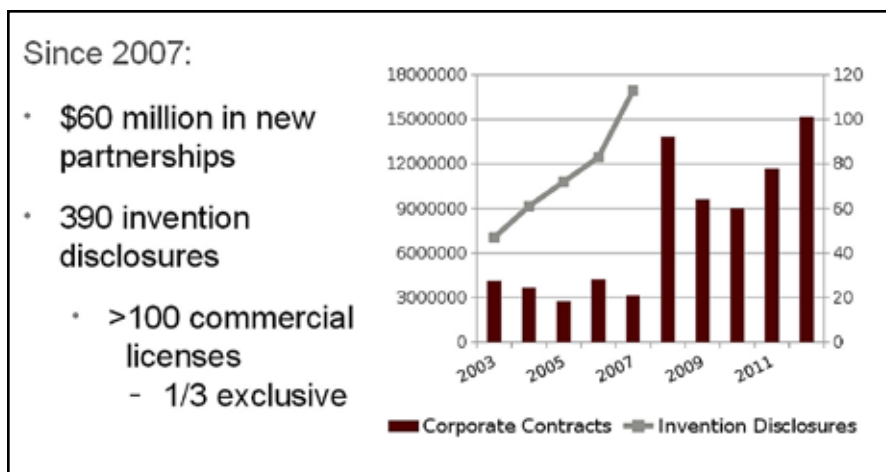


Figure 4. Generating real value.

The university is vast with much going on; it is impossible to keep track of it all. It's like Google; we invite industry: "Give us some search terms. Tell us what it is you're looking for." Then we search within the university and put things together in a way that would be an impossible task for an individual researcher to take on. We broker these relationships. We identify opportunities, and then we make sure that our partners are being taken care of and we make sure that our researchers have the opportunity to participate in audacious, ambitious projects from which amazing things develop.

Texas AgriLife Research, having assembled the personnel and resources to steward traits from discovery to commercialization, is now the number-one Texas A&M System member for disclosures, licenses and royalties.



PETER SCHUERMAN is the director of Innovation Management for Texas A&M AgriLife Research, where he works with researchers and industry to develop and execute commercialization strategies. Prior to joining AgriLife, Dr. Schureman served as the director for licensing and intellectual property for the Texas A&M University System's Office of Technology Commercialization, where he implemented novel operational procedures to achieve an unprecedented level of administrative and faculty support while significantly increasing licensing revenues and invention disclosure rates. During this time, working with AgriLife, he and his team helped the agency to develop significant industry relationships that continue to enhance its research mission.

He also served as the founder and associate director of UC Berkeley's Industry Alliances Office, a program that achieved nearly a three-fold increase in revenue from industry-sponsored research agreements in the first year of operation and specialized in closing deals in ninety days or less. He has also been a member of the commercialization programs at Rice University and the University of Florida. Schuerman has a BS in botany from Colorado State University and a PhD in genetics from UC Davis and is a USDA postdoctoral fellow.

Intellectual Property for Crop Transformation: A Continuing Saga for Agricultural Innovation in the Public Sector

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Figure 1 shows Cohen and Boyer's fundamental recombinant-DNA patent, issued in 1980. They were founders of the startup company Genentech. The patent was managed by Stanford and the University of California together. In a climate like today's, it might have been licensed exclusively to Genentech. If it had, how many biotech companies would there now be?: one! In California alone, there are 1,600. This was licensed on a non-exclusive basis for a very nominal charge. Such enabling technologies can support entire industries if they are widely available; otherwise, they support a very narrow base.

Figure 2 provides a snapshot of the intellectual-property landscape in agricultural biotechnology a few years ago. Pie A shows the landscape across the patent office as a whole, with approximately 2.5 percent assigned to the public sector. Pie B shows a very different landscape for ag-biotech, with a few large players with large intellectual-property portfolios. It has been speculated that the management of these intellectual-property portfolios has played a part in producing an industry that is relatively concentrated in a few players. Another different feature is that there is a large public-sector slice in Pie B, which is highly fragmented across universities (Pie C).

This gave rise to the formation the Public Intellectual Property Resource for Agriculture (PIPRA¹) by the Rockefeller Foundation: could it take this public-sector portfolio and do something interesting with it—use it in strategic ways to enable not only the public sector but enable industries also?

¹PIPRA enables access to public innovation. PIPRA supports innovation in agriculture, health, water, and energy technologies. In collaboration with 50+ universities and research centers and a pro bono attorney network, PIPRA provides intellectual property rights and commercialization-strategy services to increase the impact of public-sector innovation, particularly for developing countries and specialty markets.

United States Patent [19]		[11]	4,237,224
Cohen et al.		[45]	Dec. 2, 1980
[54] PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS		[57] ABSTRACT	
[75] Inventors: Stanley N. Cohen, Portola Valley; Herbert W. Boyer, Mill Valley, both of Calif.		<p>Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypic property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.</p>	
[73] Assignee: Board of Trustees of the Leland Stanford Jr. University, Stanford, Calif.			
[21] Appl. No.: 1,021			
[22] Filed: Jan. 4, 1979			

Figure 1. Cohen and Boyer's landmark patent for "producing biologically functional molecular chimeras."

The first thing that the Rockefeller Foundation asked of PIPRA was to look at enabling technologies—the vectors, promoters, selectable markers, transformation methods, including *Agrobacterium*, that can link novel traits with good germplasm. The request from the Rockefeller Foundation was to examine the public-sector portfolio to see if we could create something that has freedom to operate and could be widely used.

We started the process at the Danforth Center in St. Louis. The panel of experts who met comprised plant biologists and lawyers. The objective was to define applicable technical, legal and regulatory design parameters, similar to a standard-setting process that would be used in forming a patent pool in the electronics industry. The criteria drawn up included:

- *Agrobacterium*-mediated was preferred
- A wide range of promoters
- Clear of intellectual property (IP) blocks in the United States and elsewhere (the most essential feature)
- Plant products should be marker-free
- Desirable to have the possibility of "all plant" integrations.

We went through a process of gathering freedom-to-operate opinions from an attorney network who contributed their time on a *pro bono* basis, and then to define terms of technology and corporation into a patent pool. We formed a patent pool around these technologies, developed a transformation system, and published it (Chi-Ham *et al.*, 2012). It has been distributed to a number of public-research institutions in the United

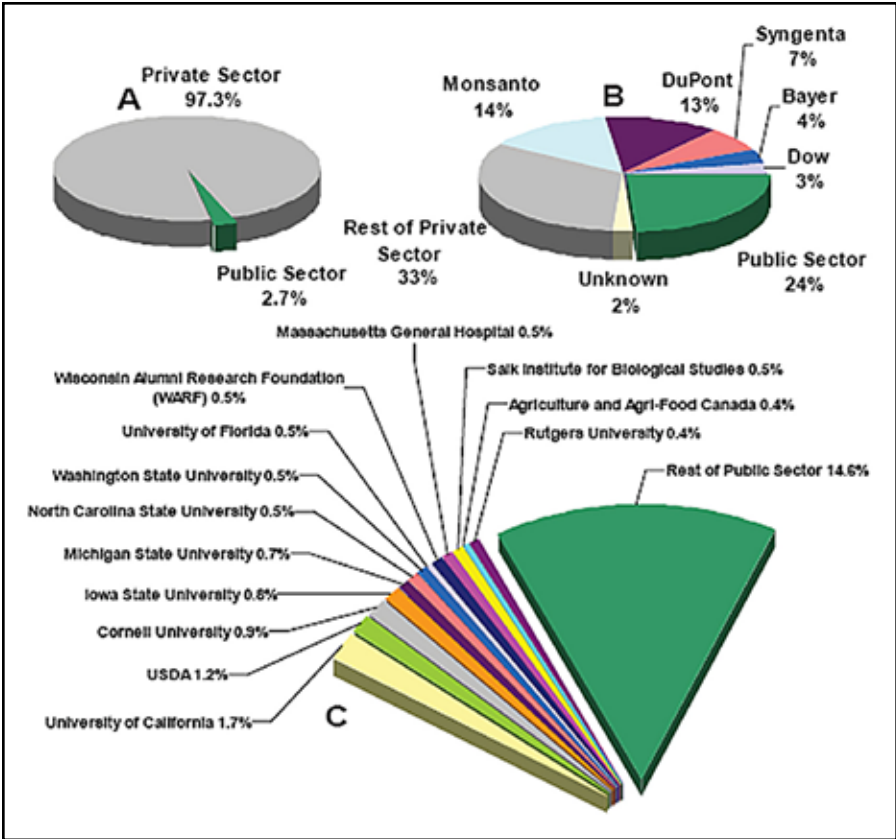


Figure 2. Recent intellectual property landscape in agricultural biotech.

States and internationally as well as to companies. Currently, it is the basis for seven trait incorporations: three that are essentially humanitarian products for Africa funded by USAID, and four commercial traits. Furthermore, the system has been used to generate a number of commercial events that are now in later-stage field-testing.

As mentioned, the published transformation system is *Agrobacterium*-based, an aspect on which the landscape has changed. Figure 3 shows the timeline of a broad and important patent application on *Agrobacterium*, filed in 1983 not only in the United States but in many other countries as well. At that particular time, in the rest of the world, patents expired 20 years after application. So, in the rest of the world this patent has expired. However, in the United States under the pre-1995 law, patents have a term of 17 years from issuance, and so it will be in force in the United States until 2029.

When we developed these vectors, it was during a period when there were no broad *Agrobacterium* patents. The ones that had existed had expired and this particular one had

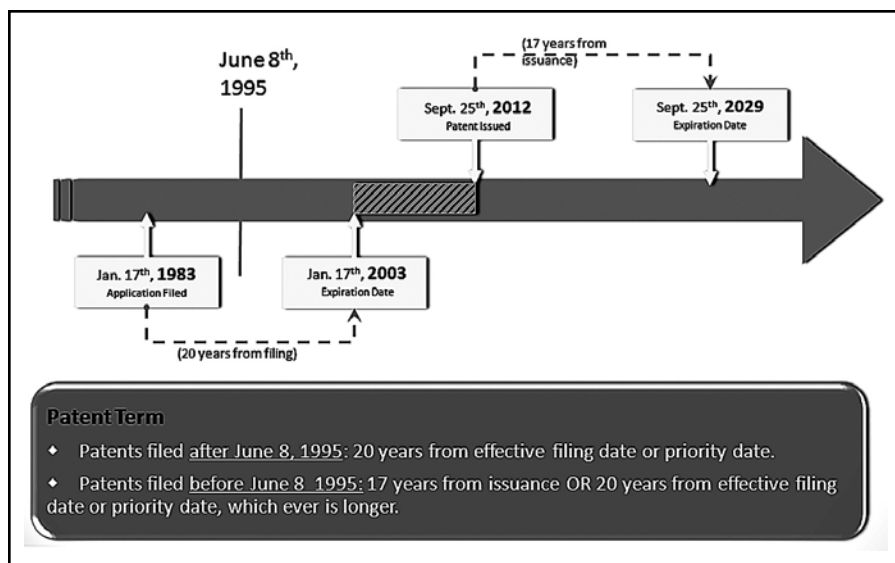


Figure 3. Over 29 years of prosecution. Anticipated expiration date: September 25, 2029.

not yet been issued. And so, this is where the landscape has changed. This very broad, well deserved, patent was issued to Monsanto on September 25, 2012 (Figure 4): *Genetically Transformed Plants*. Filed originally in 1985 as a continuation of an application filed in 1983, the patent was issued in 2012, and, as discussed above, will stay in force until 2029. University researchers who use *Agrobacterium* to transform dicots are infringing on this patent. On the other hand, Monsanto is offering a free license to academic institutions to use this methodology, which they intend to enforce. Infringing researchers are likely to hear from Monsanto. This raises the issue of the terms of that license. In fact, the conditions are reasonable and we have been working with Monsanto to improve them.

Figure 5 shows the scope of claims. It talks about genetically-transforming dicots by contact with *Agrobacterium* and incorporating *Agrobacterium* T-DNA borders; so, it's very broad.

INVENTING AROUND

The broad coverage (Figure 6, arrowed fields) has prompted examination of prospects to “invent around” (Figure 6, “X”). There may be opportunities to replace *Agrobacterium* with other bacterial genera. It talks about T-DNA from *Agrobacterium*. This suggests there may be opportunities to invent around utilizing either P-DNA or, potentially, synthetic borders. In fact, alternatives to *Agrobacterium* have been pursued for some time. In 2005, Richard Jefferson and colleagues published a paper and filed patents on using *Rhizobium* species to harbor a Ti plasmid for delivery of transgenes to plants (Figure 7). This was

(12) United States Patent Rogers et al.	(10) Patent No.: US 8,273,954 B1 (45) Date of Patent: Sep. 25, 2012
(54) GENETICALLY TRANSFORMED PLANTS	Zambryski et al, J. Mol. Appl. Genet. vol. 1 No. 8 pp. 361-370 (1982).*
(75) Inventors: Stephen G. Rogers , Webster Groves, MO (US); Robert B. Horsch , St. Louis, MO (US); Robert T. Fraley , Glendale, MO (US)	Schell et al, From Genetic Experimentation to Biotechnology—The Critical Transition edited by Whelan et al pp. 41-52 Sep. 1987.* Depicker et al, J. Mol. Appl. Genet. vol. 1 No. 6 pp. 561-573 (1982).*
(73) Assignee: Monsanto Technology LLC , St. Louis, MO (US)	Chilton et al, Stadler Symp. vol. 13 pp. 39-51 (1981).*
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	Zambryski et al, Journal of Molecular and Applied Genetics vol. 1 pp. 361-370 Jun. 1, 1982.* Depicker et al, Journal of Molecular and Applied Genetics vol. 1 pp. 501-573 Dec. 1, 1982.*
(21) Appl. No.: 06/793,486	Schell et al, From Genetic Engineering to Biotechnology—The Critical Transition, Ed. by Whelan et al, Pub Wiley & Sons pp. 41-52 (May 21, 1982).*
(22) Filed: Oct. 30, 1985	Leemans et al, Molecular Biology of Plant Tumors Ed by Kohl et al, Academic Press Inc. pp. 537-545 (1982).*
Related U.S. Application Data	
(63) Continuation of application No. 06/458,402, filed on Jan. 17, 1983, now abandoned.	Matzke et al, Journal of Molecular and Applied Genetics vol. 1 pp. 39-49 (1981).*
(51) Int. Cl. C12N 15/84 (2006.01) C12N 15/54 (2006.01)	Ottens et al, Mol. Gen Genet. vol. 183 pp. 209-213 (1981).*
(52) U.S. Cl. 800/294; 435/194; 435/469	De Greve et al, Nature vol. 300 pp. 752-754 Dec. 1982.*
(58) Field of Classification Search 435/172.3, 435/240, 30, 52	Montagu et al, Current Topics in Microbiology & Immunology vol. 96 pp. 237-254 (1982).*
See application file for complete search history.	

Figure 4. Recently issued patent.

the basis of what he called BiOS or open-innovation platform. However, efficiency was low and the concept failed to gain traction.

In 2011, a group in Ireland (led by Ewen Mullins) published on and patented *Ensifer adhaerens*—closely related to the *Rhizobium/Agrobacterium* group—claiming broad applicability for gene transfer. Figure 8 includes data generated with potato.

Another area to invent around is P-DNA or synthetic DNA borders (Figure 6), which has been the topic of important publications (Figure 9). Because we keep a watch on these things, we have noticed that one of the seminal papers on this topic has been retracted, which may affect the patent. If these move into the public domain, they would probably constitute a complete workaround.

OTHER PIPRA ACTIVITIES

PIPRA provides intellectual property support to a number of agencies and universities. One the reasons that the Rockefeller Foundation became interested in intellectual property was the Golden Rice story and the intellectual property audit that identified a large number of proprietary technologies that were infringed (Figure 10). Ingo Potrykus agrees

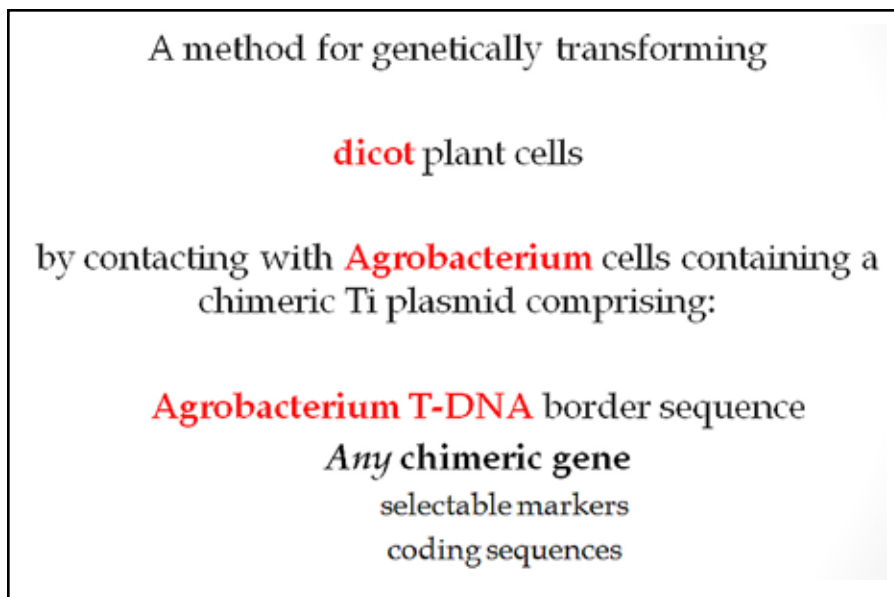


Figure 5. Patent No. 8273954, Genetically Transformed Plants: Scope of claims.

with Dennis Gonsalves² that intellectual property was not the main issue preventing the advancement of this innovation. In spite of the large number of proprietary technologies involved, it was quickly realized that Golden Rice could be “rebuilt” using approximately five proprietary technologies instead of seventy. As suggested by Scott Thenell³ regarding planning innovations to address regulatory issues, forethought may also minimize intellectual property issues. PIPRA makes a lot of freedom-to-operate assessments for public-sector projects to determine if products or processes use third-party proprietary technologies and, if so, can the project obtain the rights to those properties? We look at intellectual property landscapes and patents, but we also look at materials used and material transfer agreements, which, it turns out, are always the more problematic.

Anyone who has used a Gateway vector has agreed to the conditions set out in Figure 11. This license says that the buyer cannot sell or otherwise transfer materials made using this product or its components to a third party or for any commercial purposes.

Figure 12 provides a list of about half of our freedom-to-operate (FTO) assessments, many of which were for the Bill and Linda Gates Foundation. Others were for the Department of Energy, which is now involved in a number of projects. The common feature of these projects is that they are funding research with commercial intentions. The agencies, of course, are interested in basic findings but they also want to see products that solve real problems. As a result, they’ve gotten quite involved in looking at FTO assessments before the research starts, *i.e.* addressing up-front issues and minimizing downstream issues in these particular projects.

²Pages 37–46.

³Pages 183–194.

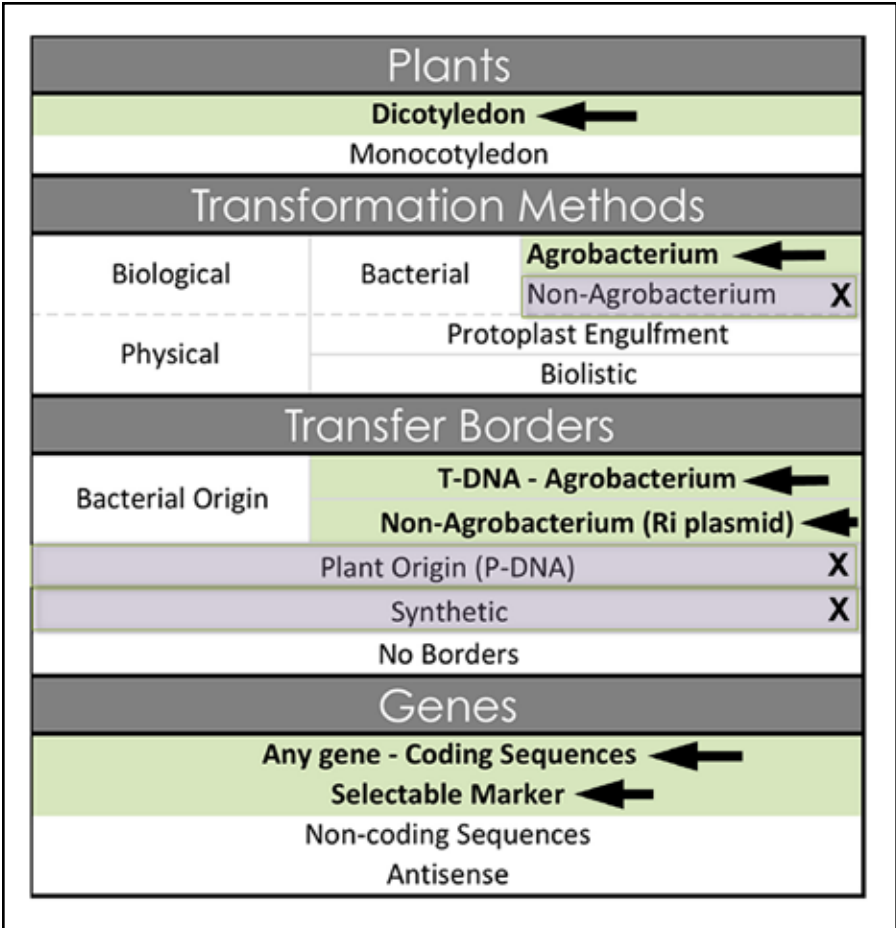


Figure 6. Preliminary analysis: Scope of claims.
Inventing Around

EDUCATION AND OUTREACH

Another area of PIPRA involvement is education and outreach. Figure 13 shows a two-volume set of *Best Practices* handbooks that we published in 2007. We run a licensing academy for technology managers from developing countries. The academy currently has forty students from twenty countries. There is great interest and significant hunger in understanding how to manage intellectual property in developing countries. Accordingly, awareness is increasing. A lot of countries are focusing on increasing their capacity so that they can address their own innovations. Not only are they interested in using our innovations, but they want to protect and exploit their own.

letters to nature

Gene transfer to plants by diverse species of bacteria

Wim Broothaerts[†], Heidi J. Mitchell[†], Brian Weir[†], Sarah Kaines^{*},
Leon M. A. Smith, Wei Yang, Jorge E. Mayer^{*}, Carolina Roa-Rodriguez^{*}
& Richard A. Jefferson

EUROPEAN PATENT APPLICATION

© 2005 C 12 N 15/00
A 01 N 1/00, C 12 N 5/09
C 12 N 1/20, C 12 P 21/02
J012N1/20, C12N1/41,
C12N1/20, C12N1/31

(19) **United States**

(12) **Patent Application Publication**

Jefferson

(10) Pub. No.: **US 2005/0289667 A1**

(43) Pub. Date: **Dec. 29, 2005**

(54) **BIOLOGICAL GENE TRANSFER SYSTEM FOR EUKARYOTIC CELLS**

(75) Inventor: **Richard A. Jefferson, Canberra (AU)**

Publication Classification


(51) Int. CL.⁷ **A01H 1/00, C12N 15/82**

(52) U.S. CL. **800/279; 800/294**

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Figure 7. Alternatives to *Agrobacterium* for gene delivery.

Project number: 5630

Funding source: Teagasc
(Agriculture and Food Development – Ireland)

Date: July, 2011


Project dates: Apr 2007 – July 2010

A novel method for the genetic transformation of plant cells

Bacteria

- Proteobacteria
 - Alphaproteobacteria
 - Brevundimonas
 - Rhizobiales
 - Phyllobacteriaceae
 - Aminobacter sp. M1-p2a
 - Mesorhizobium loti
 - Rhizobiaceae
 - Sinorhizobium/Ensifer group
 - Ensifer adhaerens *
 - Sinorhizobium meliloti
 - Rhizobium/Agrobacterium group
 - Rhizobium sp. NGR234 (rhizobium ngr234)
 - Agrobacterium tumefaciens
 - Gammaproteobacteria
 - Stenotrophomonas sp. Fa6
 - Enterobacteriaceae

E. adhaerens
Untreated
Agrobacterium



Genetic transformation of potato leaf (upper) and tuber (lower) tissues with *Ensifer adhaerens* OV14 compared to *Agrobacterium*. Blue staining indicates the presence of transformed tissues.

Figure 8. Transformation of potato with *Ensifer adhaerens*.

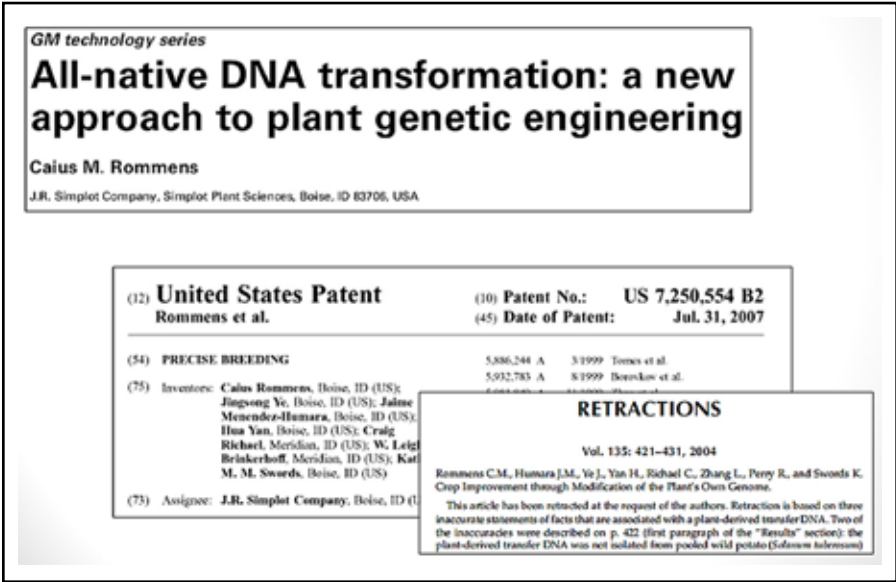


Figure 9. T-DNA replacement with “P-DNA” or synthetic DNA borders.



Figure 10. Intellectual property creates challenges for public research and missed opportunities for crop development.

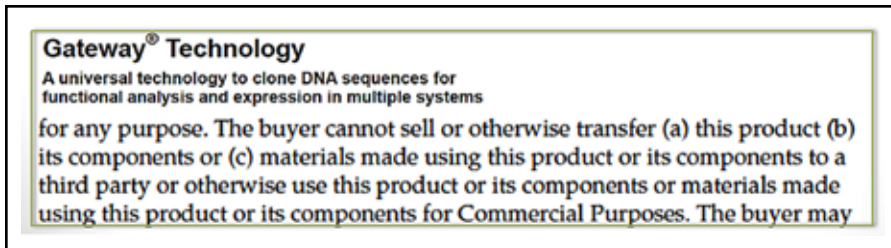


Figure 11. A “shrink wrapped” license.

Gene Patents

PIPRA is involved in a few genome projects and the issues of gene patents. Patent claims are appropriating public science at a fast pace. Figure 14 shows a famous patent application, sometimes referred to as “the patent from hell.” This is a claim for a transgenic plant having an improved trait by expressing any of these genes or any related gene with 65 percent homology. These are sometimes called “jumbo” patents.

Figure 15 illustrates the situation for *Arabidopsis*- and rice-gene patents. Those in blue (88) are patents that were issued before the public release of the *Arabidopsis* genome. Four hundred and forty patents were issued on *Arabidopsis* genes after the public release of the genome. The same applies for rice: 284 before and 832 after. This raises the issue of the implications of public release of a genome, *i.e.* putting data on the Internet that provides opportunities for appropriating gene ownership.

Genome Projects

PIPRA has been working with the cacao-genome project and will be working with other similar projects soon. The cacao genome sequence was completed a few years ago for the express purpose of making it publicly available. And so, the sponsors of this genome asked PIPRA what it means to be publicly available. We worked with them to develop a portal for this genome, which involves an information access agreement with terms and conditions:

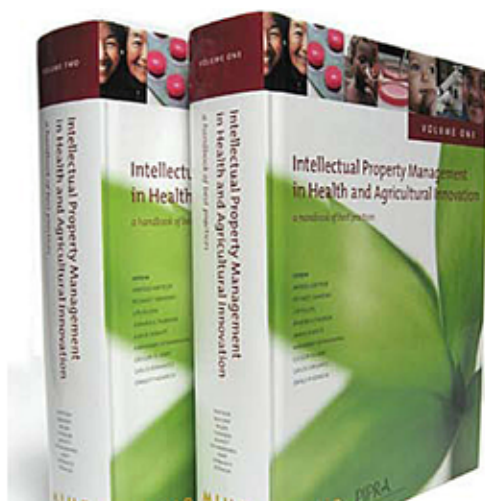
The user shall not claim legal ownership over the information and data. And the user agrees not to claim any sequences in any patent application. On the other hand, the foregoing shall not prevent the user from releasing, reproducing, seeking intellectual property protection on improved seeds or plants that are developed using this information.

The goal is to protect upstream information that can be thought of as research tools and enabling technologies to ensure that they remain publicly available and focus on protection, commercialization and exploitation of downstream products for purposes of making such seeds or plants available to farmers for cultivation.

A large multi-sponsored project is on-going to sequence the genomes of some one hundred orphan crops in Africa, with the intent of using similar portals. These all may become moot points considering that the Supreme Court may disallow patenting of genes and other naturally occurring molecules. Patenting of cDNAs and the like, which don’t occur in nature, may be allowed.

Patent Landscapes for Strategies to address Pierce's Disease in Grapes	California Department of Food and Agriculture	3 x HIV vaccine patent landscape reports	International AIDS Vaccine Initiative
Patent Landscapes for Disease Resistant Traits in Cassava	Bill and Melinda Gates Foundation Donald Danforth Plant Science Center (DDPSC), the International Institute of Tropical Agriculture (IITA)	Lignocellulosic Ethanol patent landscape report	US Department of Energy
Patent Landscapes for Disease Resistant Traits in Cassava	Bill and Melinda Gates Foundation Donald Danforth Plant Science Center (DDPSC), the National Crop Resources Research Institute (NaCRRRI), and the Kenya Agricultural Research Institute (KARI).	Stem Cell	PIPRA sponsored
Patent Landscapes for Double Haploid in Cassava	Bill and Melinda Gates Foundation International Center for Tropical Agriculture (CIAT), the International Institute of Tropical Agriculture (IITA), and the Shanghai Center for Cassava Biotechnology	HIV vaccine Upstream Technologies	PIPRA sponsored
Patent Landscapes for Disease Resistant Traits in Sweet Potato	Bill and Melinda Gates Foundation International Potato Center (Peru)	Core Technologies of four research strategies for Increase Carbon Fixation	US Department of Energy - Advanced Research Projects Agency-Energy (ARPA E); LBL, U Mass, NCSU
Patent Landscapes for Disease Resistant Traits in Wheat	Bill and Melinda Gates Foundation collaborative project with the University of California Davis (UC Davis), and a laboratory at the USDA in Albany, California.	Global Agricultural Patent Landscape (See Annex A)	Rockefeller Foundation
Patent Landscapes for Nutrition Improvement in Banana	Bill and Melinda Gates Foundation collaborative project with Queensland University of Technology (QUT) in Australia with the National Agricultural Research Organization (NARO) in Uganda.	4 x agricultural biotechnology	Rockefeller Foundation
Freedom to Operate Analysis on Ensilifer-mediated Transformation Technology	Teagasc: The Agriculture and Food Development Authority in Ireland	Sweet Potato for Africa	Howard G. Buffet Foundation

Figure 12. Freedom to operate—project assessment/enablement.



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 ... Plus an
 Executive
 Guide!

This Handbook... is a valuable guide in helping to navigate the complex—but rewarding—world of an increasingly global innovation system. — Norman Borlaug
 Nobel Peace Prize Laureate

Figure 13. *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices.*

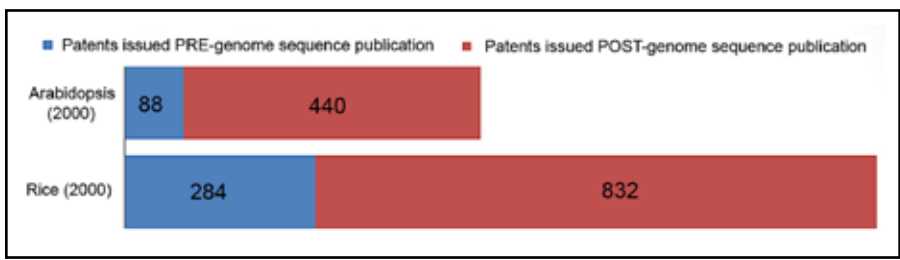


Figure 15. Number of US patents with word arabidopsis or rice in claims.

1. A transgenic plant having an improved trait relative to a control plant, wherein: (a) the transgenic plant comprises a recombinant polynucleotide encoding a first polypeptide having a conserved domain at least 65% identical to the conserved domain of a second polypeptide selected from the group consisting of SEQ ID NO: 110, 112, 116, 120, 124, 128, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171, 175, 179, 183, 187, 191, 195, 199, 203, 207, 211, 215, 219, 223, 227, 231, 235, 239, 243, 247, 251, 255, 259, 263, 267, 271, 275, 280, 284, 288, 292, 296, 299, 303, 306, 309, 313, 317, 321, 325, 329, 333, 337, 341, 345, 349, 353, 357, 361, 365, 369, 373, 377, 381, 385, 389, 393, 397, 401, 404, 406, 409, 413, 416, 419, 422, 425, 428, 431, 435, 439, 443, 447, 451, 454, 458, 462, 465, 468, 471, 475, 478, 482, 485, 489, 493, 497, 501, 505, 509, 512, 515, 519, 522, 526, 530, 534, 538, 542, 546, 550, 553, 557, 561, 565, 568, 571, 574, 577, 581, 585, 588, 591, 594, 597, 601, 605, 609, 613, 616, 620, 624, 628, 632, 636, 640, 644, 648, 652, 656, 660, 664, 667, 671, 674, 678, 682, 686, 689, 692, 696, 700, 704, 708, 712, 715, 719, 723, 727, 731, 734, 738, 741, 745, 749, 752, 756, 760, 762, 766, 770, 774, 778, 782, 786, 789, 793, 797, 801, 805, 809, 813, 816, 819, 823, 827, 831, 835, 839, 843, 847, 851, 855, 859, 863, 867, 871, 874, 878, 882, 886, 890, 894, 898, 901, 905, 909, 913, 917, 921, 925, 929, 933, 937, 941, 945, 949, 953, 957, 960, 963, 966, 970, 973, 976, 980, 984, 988, 992, 995, 999, 1003, 1007, 1011, 1015, 1019, 1023, 1027, 1031, 1037, 1041, 1045, 1049, 1052, 1056, 1060, 1064, 1067, 1071, 1075, 1078, 1081, 1085, 1089, 1093, 1097, 1101, 1104, 1108, 1112, 1116, 1120, 1123, 1126, 1130, 1134, 1138, 1142, 1145, 1148, 1151, 1154, 1157, 1161, 1165, 1169, 1173, 1177, 1181, 1185, 1188, 1192, 1195, 1199, 1203, 1207, 1211, 1215, 1219, 1222, 1226, 1229, 1233, 1236, 1240, 1243, 1247, 1251, 1254, 1258, 1262, 1266, 1269, 1273, 1277, 1281, 1285, 1289, 1293, 1297, 1300, 1304, 1308, 1311, 1314, 1318, 1322, 1326, 1330, 1334, 1338, 1342, 1346, 1350, 1354, 1358, 1361, 1365, 1369, 1372, 1376, 1380, 1384, 1388, 1392, 1396, 1400, 1404, 1408, 1411, 1415, 1419, 1423, 1427, 1431, 1435, 1439, 1443, 1446, 1449, 1452, 1455, 1459, 1463, 1467, 1470, 1474, 1477, 1481, 1488, 1492, 1495, 1499, 1503, 1507, 1511, 1515, 1519, 1522, 1526, 1530, 1533, 1537, 1541, 1545, 1549, 1553, 1557, 1561, 1565, 1568, 1572, 1576, 1579, 1583, 1586, 1589, 1593, 1596, 1598, 1602, 1604, 1608, 1611, 1614, 1617, 1620, 1624, 1628, 1632, 1636, 1640, 1645, 1648, 1652, 1656, 1660, 1664, 1668, 1672, 1676, 1680, 1684, 1688, 1692, 1696, 1700, 1704, 1707, 1711, 1715, 1719, 1722, 1726, 1729, 1733, 1737, 1741, 1745, 1749, 1753, 1757, 1761, 1765, 1769, 1773, 1777, 1781, 1785, 1789, 1793, 1796, 1800, 1803, 1806, 1809, 1812, 1816, 1820, 1824, 1827, 1831, 1835, 1838, 1841, 1844, 1846, 1850, 1853, 1857, 1861, 1865, 1869, 1873, 1877, 1881, 1885, 1889, 1893, 1897, 1901, 1904, 1908, 1912, 1916, 1920, 1924, 1928, 1932, 1935, 1939, 1943, 1949, 1957, 1961, 1964, 1967, 1970, 1973, 1977, 1981, 1984, 1986, 1988, 1990, 1992, 1994, 1996, 1998; and 1999-2007; (b) the improved trait is selected from the group consisting of larger size, larger seeds, greater yield, darker green color, increased rate of photosynthesis, more tolerance to osmotic stress, more drought tolerance, more heat tolerance, more salt tolerance, more cold tolerance, more tolerance to low nitrogen, early flowering, delayed flowering, more resistance to disease, more seed protein, and more seed oil relative to the control plant.

2. The transgenic plant of claim 1, wherein the conserved domain is at least 80% identical to the conserved domain of the second polypeptide.

Figure 14. Patent claims are appropriating public science at a fast pace.

IN SUMMARY

The intellectual-property landscape for transformation has shifted. Sponsors of translational research are increasingly interested in clearing IP barriers in advance of making grant awards. And plant-gene patents may become moot, if the Supreme Court rules similarly to their opinion on human genes.

REFERENCE

Chi-Ham CL *et al.* (2012) An intellectual property sharing initiative in agricultural biotechnology: development of broad accessible technologies for plant transformation. *Plant Biotechnology Journal* 10(5) 501–510.



ALAN BENNETT is professor of plant sciences at the University of California, Davis. He earned BS and PhD degrees in plant biology at UC Davis and Cornell University, respectively, and has over 160 publications. His research has focused on molecular biology of tomato-fruit development and ripening; cell-wall disassembly; and intellectual property rights in agriculture. He is a fellow of the American Association for the Advancement of Science and a senior fellow of the California Council for Science and Technology. He has also served in a range of leadership positions at the University of California, including department chair, divisional associate dean in the College of Agricultural and Environmental Sciences, UC system-wide executive director of research administration and technology transfer, and associate vice chancellor for research at Davis. In these capacities, he has been responsible for research and teaching budgets, for establishing and overseeing research policy, and for the management of a portfolio of over 5,000 patented inventions, 700 active licenses and revenue in excess of \$350 million.

In 2004, Dr. Bennett founded the Public Intellectual Property Resource for Agriculture (PIPRA) to accelerate the deployment of public-sector technologies for specialty and subsistence crops in developing countries. PIPRA has been supported by the Rockefeller and Bill & Melinda Gates Foundations as well as by numerous government agencies and private companies.

Session 3-2: The Regulatory Process and Technology Access for Specialty Crops

Q&A

MODERATOR: DAVID BALTENSPERGER

Texas A&M University

College Station, Texas

Erik Mirkov (Texas A&M University, College Station): Alan, what is your opinion on not only the September 25 Monsanto patent but also the one issued December 18? Do you see coexistence with the Syngenta patents?

Alan Bennett: I think I know the Syngenta patents you are talking about—I thought they had expired. They originally came from Washington University, I think. I'm not sure about coexistence. Sorry.

Roger Beachy (Global Institute for Food Security, Saskatoon): What chance is there that Monsanto will do a "Cohen and Boyer"?

Bennett: Little, but I think they should be encouraged to.

Beachy: Absolutely. That's the point. This is terribly important. It's an enabler just like the "Cohen and Boyer" patent was. That's what the industry needs. Are we going to play in sandboxes or are we going to play in the big field?

Bennett: Yes, the landscape has changed so much. The intellectual property portfolio—key patents that Monsanto had—were really important in establishing them in the industry in a very strong position. Clearly, those tools are not valuable in the same way today, and enabling an entire industry might be to everyone's advantage, including Monsanto's.

Tom Redick (Global Environmental Ethics Council, Clayton): Scott, a question mostly for you. I'm the guy who started major market approval as a big problem for all the sick sisters of biotech and we are starting to talk about whether certain closed-loop¹ identity-preserved production models could work for, say, a specialty crop. I'm wondering, is there a way we could carve out a corner of the world where we could grow it in a confined district in a confined production system so that we don't interfere with the markets overseas?

Scott Thenell: Tom, you are probably right that it can be done with a considerable amount of planning, and reassurance for trading partners that it is robust. Also from a regulatory approval standpoint, yes, if you can develop a robust identity-preservation closed-loop system, then I think you can.

Tim Hall (Texas A&M University, College Station): It was mentioned that the Monsanto *Agrobacterium* patent was very strong and very solid for dicot crops. Do you think it is equally strong for monocots, considering that it has been found to be extremely good in rice, for example?

Bennett: That particular patent is specific for dicots. Other strong monocot patents exist as well, but this is not one of them.

Hall: For monocots? *Agrobacterium*-mediated? When you say there are other systems, other patents, do you mean including *Agrobacterium*-mediated?

Bennett: Yes, *Agrobacterium*-mediated transformation in monocots—strong patents exist.

Peter Schuerman: One of the questions we get a lot within the university is about whether or not a patent might be a problem. It's very easy to think about patents as problems rather than as opportunities. Universities got into the patent system about 100 years too late. We've been innovating the whole time, but better late than never. A patent is an opportunity for a conversation. A kind of conversation that universities aren't used to having. If what you want to do infringes on someone else's rights, you can talk to that someone else and say, "Here is how it's beneficial to both of us," then it is not a problem, it's an opportunity.

Bennett: That's a good point. Dennis Gonsalves² has experienced that. When he had a product, it was clear what it was, he went to the patent owners: not a problem. But I'm going to refer to one of your slides, Peter, where there was uncertainty for the investigator—uncertainty as to whether something would work out or not. "Should I even start down that path?" That's the other issue with patent portfolios: they cloud the future.

¹Closed loop: see pages 223, 225 and 256.

²Pages 37–46.

Session 4: Perspectives from Relevant Groups

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The “Stacked” Pipeline of Biotech Specialty Crops and Regulatory/Market Barriers to Coexistence

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The pipelines for new specialty biotech crops are jammed with new varieties, many of which bring long-awaited consumer benefits. While sweet corn, potato, and squash have made it to market, barriers await this innovation. These include regulations, export-trade objections, a few ill-conceived sustainability standards and continuing consumer or food-manufacturer resistance. Some new forms of plant breeding may evade some regulations in the United States, but face regulatory barriers in wary overseas markets. These markets have trade barriers arising from the European Union’s traceability directive, which implements the 2003 Cartagena Protocol on Biosafety (“Biosafety Protocol”), an international law driving “precautionary” laws worldwide.

In the commodity-crop sector, the innovation pipeline is stacking up in two different ways, and the specialty sector will probably fall into the same pattern. First, companies stack events by putting two or more genetic events in a biotech crop. Second, regulatory approvals are stacking up, as the pace of innovation is straining US and global regulatory capacity to regulate in a timely, functional manner. With some nations also requiring approvals of stacks, the regulatory approvals of stacked crops will be stacked up like cars in line at a freeway on-ramp at rush hour.

The next ten to twenty years will be key in the transition to a fully functional global marketplace that accepts specialty and commodity biotech crops. Depending on the level of export-dependency (*e.g.* corn, soybean, canola, cotton) there will be new stacked specialty crops that are grown in containment without approval in every significant market with a functioning approval system.

Specialty crops will also benefit from new plant-breeding methods that do not use the traditional recombinant-DNA viral vectors, like RNA silencing or interference (RNAi) and all the other plant-breeding methods—directed oligonucleotides, zinc fingers, methylation along an epigenetic chromosome, and others. At the present time, various nations are evaluating how these methods will be regulated.

Unfortunately, regardless of scientific reasons to see less risk, some new plant-breeding methods will prove objectionable to anti-GMO activists. In fact, activists are already targeting “excessive RNA” in some breeding processes. Unfortunately, new plant-breeding methods will not get a “hall pass” and avoid all regulations, even if scientists show they are more precise and even with genes from within the same plant’s genome (*i.e.* “cisgenic”).

One of the most complex emerging legal issues is the expiration of patents along with expiring approvals. Biotech crops go off-patent in 20 years or so, so be sure to consult an attorney on actual expiration dates. With that in mind, check approvals in key nations where approvals are time-limited (Europe, China, *etc.*). Roundup-Ready soybean, for example, needs renewal of approval for food/feed use every three years in China. Monsanto presents new scientific data rebutting environmental concerns and health risks, spending millions of dollars annually to maintain such approvals. After patents expire, who will renew approval for the “generic” version, if Monsanto or another seed company does not help? Fortunately, a new industry stewardship program, the “AgAccord” (2014a) offers a new agreement on “Data Use and Compensation” (AgAccord, 2014b).

Lastly, sustainability is a whole new barrier to entry that everyone is talking about and some are trying to define. Unfortunately, when Europe talks about sustainability, it usually means, “How can we stop American corn and soybeans from being shipped here and made into biofuels?” Sustainability will continue to be hard to define. Applying SWOT analysis, sustainability is both an opportunity and a threat (Job, 2012). Specialty biotech crops may be more sustainable. For example, a new specialty soybean—producing high-oleic oil—offers a more sustainable carbon footprint during its life cycle because you can cook twice as many French fries; it lasts longer in the fryer.

DEFINING AND SUPPORTING SPECIALTY CROPS

For purposes of regulation, the term “specialty crops” was defined and litigated 120 years ago in a Supreme Court case involving the 1883 Tariff Act which taxed imported vegetables, not fruit. In *Nix v. Hedden* (1893), the US Supreme Court ruled on that still-debated question: Is the tomato a vegetable or a fruit? The Supreme Court said vegetable; the law does not particularly care what a botanist might say on this topic, as they were lawyers who became judges appointed for life.

USDA defines specialty in a broad sense. For example, edamame—a soybean grown in small identity-preserved amounts and hand-picked—is a specialty crop unlike its cousin, the commodity soybean, which is grown in massive amounts. Although USDA actually funded edamame to be grown in the United States, 97% is imported, mostly from Asia (Roseboro, 2012). Amid the commodity sector of corn, soy and canola, biotech crops may be grown via a “specialty” production process. Specialized oils, specialized corn, specialized

canola and other crops are grown in identity-preserved loops to maintain purity, and are produced on smaller scales than the blockbuster commodity crops with input traits that over 90% of growers want.

USDA (USDA-NIFA, 2013) has a specialty-crop research initiative that probably could be used for specialty GM crops and to the extent it continues to be funded under the new Farm Bill, this sector should apply to use those funds.

At last count, biotech sweet corn had 40 percent of the market, and biotech papaya is firmly established in Hawaii. In some respects, biotech specialty-crop production is, therefore, booming, and similar gains may be seen with the Simplot potato¹.

Food manufacturers and retailers are the last hurdle, however, and specialty crops face high barriers in some corners of the market. McDonalds rejected *Bt* potatoes ten years ago; will they serve Simplot's low-acrylamide potato, with its health benefit? On the positive side, Wal-Mart is stocking biotech sweet corn. But, even Wal-Mart might balk at the GMO onion, potato or other specialty crops if there is sufficient consumer backlash. It is important to remember that even if a biotech specialty crop can get the food manufacturers to accept it, it may not last in the marketplace, because some consumers may not want to buy any "GMO." Even some successful products lose the battle for shelf space after a short run of popularity.

BIOTECH BENEFITS AND THE UPCOMING PIPELINE

It is now clear that agricultural biotechnology has provided benefits both to human health and to the environment. This continues to be clear, despite what activists say, since growers are using fewer chemicals such as pesticides. Some of the major US-based environmental groups are starting to get behind agricultural biotechnology. In a speech to a European audience in 2012, the vice president of the Worldwide Fund for Nature (WWF-US) in the United States said, "I'm convinced that modern genetic technology could help get better yields from local and regional crops in Africa and South-East Asia" (McEwan, 2012)

We have improved food safety through use of biotech corn. Iowa State University has done excellent research showing that mycotoxin formation is reduced in certain *Bt*-corn varieties. It is unhealthy to eat known carcinogens. If other nations struggling to cope with mycotoxin-related effects (cancer, birth defects, *etc.*), simply by approving planting of *Bt* corn those nations would reduce those effects and bring health benefits through biotechnology. (Murillo-Williams and Munkvold, 2008).

Moreover, time has trumped the early concerns expressed by Al Gore about biotech crops exacerbating over-supply; we know now that the world has become too needy to be cavalier in dismissing innovation in agricultural biotechnology. With people around the world asking for more and more corn, soy and other foods at reasonable prices, and rioting to overthrow their governments, we know that yields actually matter. While many factors were contributory, the recent violent protests in North Africa and the Middle East coincided with sudden peaks in global food prices. Researchers suggest that a given food-

¹Pages 97–109.

price threshold may exist, above which protests become likely (Lagi *et al.*, 2011). With such social unrest making the world an increasingly unstable place, we do not have the luxury of tinkering with the highly productive US agricultural system that makes food for the world without risking serious negative impacts overseas.

The pipeline for biotech crops is becoming more interesting with each innovation in plant breeding. Genes are being silenced with no “plant pest” DNA to regulate or test for, making regulation more complex. Such new plant-breeding methods involve:

- RNA-interference.
- Oligo-RNA *etc*—Cibus, Keygene, *etc.*
- Public-academic breeding coming on fast?
- USDA does not see a plant pest, EPA sees resistance issues, *etc.*

The pipeline of biotech commodity crops promises new approaches to food and agriculture, and, finally, direct consumer benefits, not just improved production traits (*e.g.* herbicide and pest resistance) enabling more-efficient production. These include:

- Improved consumer health (high oleic, omega-3 soy, *etc.*)
- Stress-tolerant cultivars, possibly N₂-fixing corn
- Environmental impact management—lower GHG emissions
- Feeds to reduce feedlot waste (by manipulating genes for phytase to increase efficiency of consumption of phosphates)
- More crop from a drop—drought-tolerance in time for climate-disrupted agriculture.

Although some proposed innovations may prove to be mere pipedreams, people are working on N₂ fixation in corn with symbiotic microorganisms and also making corn photosynthesis work for soy (*i.e.* “C4 soy”) (Buchanan *et al.*, 2010). There will be more room for public and academic breeding tools in the smaller specialized sector of agriculture.

All of this innovation has environmental and economic benefits. This has led the World Wildlife Fund, Environmental Defense Council, and even the Natural Resources Defense Council to start talking about technology neutrality *vis-à-vis* biotech crops.

Opposition to GMOs keeps coming and coming, however. The recently withdrawn French Séralini study, which showed tumors in rats, serves to demonstrate the commitment of certain researchers to bend scientific rules to achieve anti-GMO results. Although the study was badly flawed, it has caused governments to say, “Well, that’s peer-reviewed science. Let’s ban it and make nations stop exporting it to us.”

While the high cost of regulatory compliance has led to oligopoly power with a “concentration” in the biotech-seed marketplace, the coming decade may see more new players entering the marketplace (*e.g.* Okanagan Specialty Crops with its Arctic® Apple², and J.R. Simplot with its “Innate®” potato¹).

²Pages 87–94.

SEED INDUSTRY STEWARDSHIP COORDINATES WITH GROWER ASSOCIATIONS

The leading grower associations in US commodity corn, soybean and cotton production have established important working relationships with the biotech seed companies to keep the potentially adverse impacts of coexistence under better control. Detailed stewardship plans are created and the growers associations survey members and communicate to ensure compliance at a high level. This helps overseas buyers learn to trust the representations made in the United States regarding the “commercial launch” of new biotech crops and containment of biotech crops grown in field trials or “closed loop identity preservation” (Abramson and Carrato, 2001; BIO, 2014).

Overseas Approvals and the Biosafety Protocol

The Biosafety Protocol now has 166 parties and the 2010 Nagoya-Kuala Lumpur Supplemental Protocol on liability remains short of the ratifications needed to enter into force (NKLS, 2010). This law regulates “living modified organisms” (LMOs) which is their unique term for GMO. Under a 2006 WTO decision involving the United States, Argentina and Canada against the European Union, the WTO held that the EU and nations that have signed that law cannot apply it with its “precautionary approach” to regulatory approval against the nonparty grain- and oilseed-exporting nations. The United States is not going to sign on to a law that creates trade barriers, although the US seed and grain industries support ratification as a tool to give the United States a stronger direct voice in implementation decisions.

One area where implementation is troubling is Biosafety Protocol Article 18.2(a) with its “May contain LMOs” requirement. The EU law implementing this article, the 2004 Traceability Directive, targets that possible presence of “LMOs” and tests for events that are not approved, which forces the grain trader to declare all events contained in its shipment on the shipping documents. This law enables testing and traceback liability (see below, LibertyLink rice nuisance litigation). Such trade disruption between the Americas and the European Union has become increasingly common, with Europe’s own economists measuring billions of dollars in lost value to US corn and soybean exports (Bernauer, 2003). This has forced food manufacturers in Europe to substitute non-GMO inputs and billions of dollars in US trade has been lost.

Trade is often disrupted when events face regulatory delays, in the United States and abroad, and those delays make a stacked-up line of events that wait for approval. In a growing number of nations, the regulators add another level of regulation for stacks, requiring regulatory approval for both the events and the stack. Many nations are regulating (*e.g.* Canada) or considering regulating (European Union, Japan, *etc.*) biotech events that are not “plant pests” nor “plant incorporated protectants” and do not involve recombinant-DNA methods. These ever-shifting variations in regulatory approach can surprise plant breeders, particularly in the United States where stacks and new plant-breeding tools are not necessarily regulated. Uncertainty over global regulation is impeding investment in new breeding tools; investors really need to know what it will cost to get to market.

Anti-biotech activists are writing papers opposing new plant-breeding methods. Jack Heinemann, with an academic appointment in New Zealand, has claimed in a peer-

reviewed journal that RNA is overproduced in these crops (Heinemann *et al.*, 2013). The new plant-breeding technologies will not lack for “anti” attacks.

Depending on the scale of production and importance of the export, some biotech specialty crops may be grown without major market approvals. After USDA approval (“deregulation”) and perhaps also EPA approval (for any “plant-incorporated protectant”), it may be acceptable to the supply chain to have identity-preserved, fully contained production without obtaining overseas approval.

This may be necessary where overseas approval is very difficult to obtain, for example in China. Unfortunately, China is borderline functioning in terms of approval (*e.g.* China’s delay of over three years in approving Syngenta’s MIR 162 corn event). They do not let companies even file for approval until the applicant has been approved for use in at least one exporting nation. This is not like other countries where an applicant can make parallel submissions to multiple regulatory agencies.

Patent and Approval Expiration—the AgAccord

China is also a place where approvals expire. In Argentina, they’ve been thinking about approval expiration, in combination with patent approval expiration, for quite some time, suggesting that companies should step up and help these generic crops get approval renewal (Lema and Lowenstein, 2008).

The AgAccord (2014a) is a voluntary industry agreement that sets up a data-compensation system. A generic off-patent biotech crop can have its approval renewed if the specialty-crop breeder buys the data, using an arbitrator if value is disputed. With those data, specialty crops (blueberries, raspberries, *etc.*) could contain the Roundup-tolerance gene in coming years.

Monsanto did the right thing on post-patent issues by agreeing to keep Roundup Ready traits approved until 2021 in China, Europe and elsewhere, unless someone relieves them via the AgAccord. While Monsanto offered seven years’ worth of costly voluntary stewardship, other biotech seed companies will provide less than half of that commitment under AgAccord. This industry agreement would work for specialty crops to allow companies to share data and maintain approvals for a few years while the generic industry gets off the ground (AgAccord, 2014b).

There is a good reason for this stewardship. If Europe and China had approvals that expired, the expired Roundup-Ready events could readily disrupt trade. A 2008 University of Illinois economic study estimated, after price equilibrium, loss of income of \$15 billion a year if Europe and China were to go off-approval on a soybean grown in America (Paulson *et al.*, 2008).

For specialty biotech crops that are paired with generic herbicide resistance, such stacks of proprietary-plus-generic traits could create potentially huge opportunities in the marketplace after 2020. Indeed, all innovation in specialty biotech crops could make use of this free genetic event, but researchers have to be aware of any major threats of disrupting trade in the particular market where they will be selling their specialty crop. As the biotech-plum producers discovered, GM plums may be exported as prunes and may upset consumers overseas.

Stacks involving multiple traits are increasingly seen in the commodity-crop sector, and agricultural biotechnology in the specialty-crop sector should also stack, particularly in light of royalty-free generic events as older events go off-patent. Roundup-resistant-crop patents all expire in April 2015 in the United States (Monsanto, 2012). The patents expired already in Canada in 2011 and Canadian plant breeders may already be well along in breeding generic traits into commodity or specialty crops, getting stacked events ready for market.

Growers have been clamoring for Roundup Ready wheat for years, and specialty-crop growers share similar interests in weed control. These resistance genes could add value in carrots and some onions, which may enter the market as free “generics.” With the added-value of a generic royalty-free trait, the stack could give the public benefits.

Compact for Biodiversity Harm

On the liability issues under the Biosafety Protocol, the Nagoya-Kuala Lumpur Supplemental Protocol (2010) on LMO environmental liability law had a parallel industry compensation plan, the “Compact” that allowed that law to pass. The industry Compact is a voluntary contractual compensation mechanism established by industry to compensate and remediate any future damage to biological diversity that may be caused by an LMO (CropLife International, 2014).

In the Compact, companies agreed to have arbitrators determine whether harm to biodiversity occurred and to write checks to compensate parties to the treaty. They will remediate any harm to biodiversity from biotech crops. They deserve applause for this, and, indeed, announcement of the Compact received a standing ovation at a Cartagena, Colombia, conference.

As is noted above, the same US seed industry is also leading the way on the voluntary post-patent AgAccord. In the Compact and AgAccord, the biotech seed industry has stepped up and offered the world voluntary arbitration approaches to two complex threats to the environment and industry’s bottom lines.

Adverse Economic Impacts Lead to NEPA and Nuisance

The National Environmental Policy Act (NEPA) looms over US approval; this goes beyond USDA’s narrow “plant pest” authority to require consideration of the economic impacts to organic or non-GMO growers or the environmental impacts of glyphosate-resistant weeds. The Supreme Court reversed a lower court nationwide injunction, but also held that USDA failed to justify adequately its “finding of no significant impact” (FONSI) for the commercial launch of Monsanto’s biotech Roundup-Ready alfalfa, citing adverse “contamination” impacts including non-GMO contracts for exporters of alfalfa. Since then, however, beet sugar fortunately made it past a NEPA lawsuit to take 95 percent of US market share.

In addition to the NEPA litigation noted above, in Canada they have lawsuits called “Anticipatory Nuisance” that allows a suit against a threatened nuisance, including one involving biotech crops. As a regulation of economic impact, it has parallels to NEPA, but uses state common law to compensate growers. Nuisances are entirely economic in nature, not in terms of personal injury.

Nuisance litigation often follows the economic impact of biotech crops, real or perceived. Monsanto's isolated rogue field-trial wheat made an appearance in Oregon recently, and many lawsuits are pending for negligence and nuisance over lost export markets and adverse price impacts, which are consolidated in a Kansas federal court.

A landmark, still-pending nuisance suit involves Bayer CropScience and LibertyLink rice. US rice exports are at most a \$200 million market. This is being settled for over a billion dollars, which means litigation gives a five-times multiplier over the actual economic impact that can reasonably be measured.

Sustainability

The final barrier to entry could come from sustainability demands. This is also a door to be opened if a new stack elicits environmental or health challenges. The sustainability standards that I have seen could be technology neutral, or they could eliminate GMOs entirely. Some standards ban GMOs in midstream, like the Green Building Council, which suddenly came out of the woodwork with "no GMO wood" because the Forest Stewardship Council (FSC) was thinking ahead to the day when biotech trees might arrive.

If producers of specialty-biotech crops do not maintain vigilance, various standard-setting initiatives could encourage entire industries to ban GMOs. This is being attempted in the draft national standard on sustainable agriculture by the Leonardo Academy (2013) in Wisconsin, where a committee with organic advocates published a draft standard for public comment through April 6, 2014, with what may be interpreted as anti-GMO clauses.

CONCLUSION

Biotech specialty crops face a number of potential barriers. Regulatory uncertainty over new plant-breeding methods and costly overseas approvals could complicate plans for commercialization. Stacking a generic crop aids innovators in the marketplace, but generic crops may need the regulatory data held by patent holders to achieve regulatory approval. Sustainability standards may arbitrarily deny use of biotechnology. Any innovator heading into this sector will need to be aware of all the potential threats awaiting these exciting opportunities in genetic engineering of biotech crops.

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Genetically Engineered Specialty Crops Need Regulatory Assistance

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Four categories present, or have presented, obstacles or limitations to commercializing genetically modified (GM) specialty crops:

- **The technology itself.** Could we actually identify genes encoding useful traits, clone those genes, transfer them into the cells of specialty crop species *in vitro*, and then regenerate whole plants and have them express those traits at commercially viable levels? We know that that's pretty well overcome. We can transform virtually anything with any piece of DNA, or RNA for that matter.
- **Intellectual property**, including patents on genes and on the fundamental enabling technologies that were held largely by big companies or tied up in litigation. I know many public scientists who have said, "I can't use this technology because it's patented." Some said, "I'm using this technology, although it's patented. So don't tell anybody." We continue to have to respect intellectual property (IP) rights and I certainly encourage everyone to do that. Furthermore, companies that hold the patents are often amenable to negotiation. If you have a good idea—a good product in a specialty crop—and a patent holder isn't actively working in that area, they will probably be reasonably receptive to developing a license or some other freedom to operate. Also, patents for many of these products and enabling technologies are expiring. They may not be first-choice state-of-the-art technologies, but older approaches can be adapted and efficiency improved to get the final product that you're interested in. So, IP is not the obstacle that it used to be.

- **Public acceptance** is not the issue that a lot of people think it is. Several different groups say, “We speak for the public, and we, the public, don’t like GM organisms, so don’t develop them and don’t release them. If you put them out there, we won’t buy them, therefore, let’s ban them so that people don’t have to worry about them.” I haven’t done a sociological study on this, but, after dealing with the public for 20 years or so, I’d say that about 15 percent of the public definitely will not buy a GM fruit or vegetable in the marketplace. Dennis Gonsalves has suggested it may be 8 percent. Other people will come up with other figures, But it’s on that order 8 to 10 to 15 percent—people who say that they really don’t like GM organisms (GMOs), and then actually follow through. A lot of people say that they don’t like GMOs but buy them anyway, knowing full well what they are. They see what the price is, what the quality is, and that other people are buying them and are not dropping dead in the street. The best way to measure public acceptance is not to listen to activist groups, or any academic for that matter. The best way to measure it is to put the products in the market and let the people show you by whether they buy them. When people are given that actual real-life opportunity, for the most part they buy them. We do have GM papayas, we do have GM sweet corn, and other examples here and there. And there’s little problem once people are actually allowed to make the choice on their own directly, to buy the product today or not.
- **The federal regulatory system**, which is what I will discuss mostly.

SPECIALTY CROP REGULATORY ASSISTANCE PROGRAM

The chief obstacle to getting GM fruits and vegetables onto the market, is the regulatory system. Several years ago, a group of us, largely from the federal regulatory agencies said:

The genetically modified products on the market now are, in large part, major crops: corn, soybean, cotton, and canola, all from large companies. On the other hand, hundreds of millions of dollars of taxpayers’ money have supported the development of genetically modified specialty crops in our public institutions, in USDA, in our universities and other not-for-profit organizations, plus small companies. Where are the results of that effort? Did all of those projects fail? Was it a waste of money?

A meeting was called in Washington to address whether there was interest in joining forces, either formally or informally, large or small, to promote the use of genetic technologies for improvement of specialty crops. It emerged that there was a great deal of interest. Passionate about the technology, people wanted to develop products that big companies probably wouldn’t be interested in: public-good, high-value items, that don’t necessarily have sufficient dollar value to generate industry interest in terms of profit but would be good for the environment, for society and for human health. This passionate interest existed mostly in small-company and public-sector scientists.

We discussed ways to facilitate regulatory clearance because of the broadly held view that achieving deregulation was a major stumbling block. The Specialty Crop Regulatory Assistance (SCRA) program was set up in 2004, under the auspices of which we have held several meetings, mostly workshops that have included developers of GM specialty crops and representatives of the regulatory agencies. With seed money from the secretary of agriculture, we hired Kellye Eversole, in DC, who has been involved in this effort ever since. We have moved forward with a number of initiatives. Several workshop-type meetings have:

- Examined the regulatory system, including the hoops a developer has to jump through, and
- Explored costs, obviously a major issue for everyone.

COST OF GAINING REGULATORY APPROVAL

Discussions at this conference have questioned the actual cost of gaining regulatory approval; is it \$50 million to \$100 million as some companies have indicated? We have learned that it isn't necessarily that expensive. You have to calculate the cost above and beyond the routine R&D involved in producing a new crop variety, which comes down to an interesting accounting exercise. When I developed a transgenic flax many years ago, I worked at a major plant-breeding institution. We had huge farms and research plots, and several teams evaluated the project, supervising seeding, harvesting, quality analyses, chemical analyses, amino acid analyses, and performing efficacy and yield trials. All of these functions were part of a large infrastructure within which my lines were tested. Tens of thousands of lines of various species underwent tests, all within the same infrastructure. It was virtually impossible to determine my segment of the overall bill. Furthermore, if this were not a GM product, but a conventionally bred variety of the same crop type, how much would that have cost? And then, how much in addition has to be spent to generate the additional data required by regulatory agencies for appraisal of a GM trait? When you do those calculations, the marginal cost comes down to the order of a few tens of thousands of dollars.

When Dennis Gonsalves¹ and I compared notes—his papaya and my flax went through the regulatory system at approximately the same time—we came up with similar figures. Of course, nowadays, it is likely that neither Dennis's papaya nor my flax would get through the regulatory system; it is that much more onerous than it was in the mid-1990s. But, don't believe those \$50 million price tags that are thrown out. It can be done a lot less expensively, and one of the things that we've learned during our various workshops is the need to talk to the regulators themselves, which is the best way to find out what's actually needed. There are ways to satisfy the requirements without necessarily doing what you think you might have to do in terms of additional experimentation or field trials or feeding tests on humans for ten years, *etc.* You may be surprised to learn that you can achieve deregulation without investing a lot of time and/or spending a lot of money.

¹Pages 37–46.

MODELING ON IR-4

We wanted to set up a structure similar to that of the IR-4 program or the FDA's orphan drug program, recognizing that many specialty crops are of insufficient value in terms of market size to justify full-blown costs of deregulation. We thought that it would be useful to propose an institution, modeled particularly after IR-4, within which the SCRA program would sponsor a given GM specialty crop event or variety, and actually carry it through the regulatory system to obtain approvals. Although IR-4 works through EPA, the program is based in USDA. And in our situation with SCRA, it could involve our taking this product to all three of the regulatory agencies and navigating the system, so that the developer—a university-based person or from a small company—wouldn't bear the total cost. It would be largely subsidized. We're not looking for shortcuts here in terms of exemptions from requirements, but rather rationalizing and organizing the dossier so that it meets the requirements, and we have assurance of safety of the product, but without "bells and whistles" that may be attached to some of the other dossiers that our regulators see.

We decided to focus on the US regulatory system. Many US products are sent overseas; we have trading partners in various countries and regions. There was no point in getting approval in the United States for a product that served a large export market. Also, we are more familiar with the US regulations and majority of our members are in this country. There is good coordination between the Canadian and US regulatory systems. Although differences exist in legislation and the regulations themselves, the same data package can be used, to a great extent, in both Canada and the United States. That certainly was true with my flax. We decided that Europe was schizophrenic and paranoid when it came to GMOs. They ignore their own laws, so there was no point in going through the European Food Safety Authority (EFSA) system and getting an approval only to have some member countries initiate a ban anyway.

At the SCRA, we have our own expertise, provided by plant breeders, molecular geneticists, people who are experienced in the regulatory system, and political people who know how the machinery works in Washington. We also have several consultants to help individual entities. At our last workshop 18 months ago, we had a session at which we provided access to consultants experienced in dealing with our regulatory system and our regulators. We also brought in regulators, *i.e.* not policy people necessarily—they were there as well—but agency people who actually work hands-on with dossiers, whose job it is to come in every morning and see a stack of papers saying, "Here's yet another *Bt* corn for you to evaluate." We conducted this workshop under Chatham House Rules—*i.e.* confidential with no attribution—which lends itself to people saying things that they wouldn't say in a public setting or in a conventional workshop. They didn't want to be in a situation where they could be quoted later: "You told us at that workshop that we could provide this data set instead of that data set," when in actuality they said, "Well, we're thinking about maybe this or maybe that, or here's a tentative idea. What do you think?" We wanted fresh ideas without necessarily holding the speakers to those ideas.

It was a great success. Comments received afterwards were enlightening. A number of people said that it was the best workshop they had ever attended, having learned more than at any other workshop or conferences, and that the information was really useful, due to communication between the developers and the consultants, and between the developers and the regulators, the people who actually do hands-on work with the dossiers. A similar workshop is planned.

Attempts continue to secure long-term funding to maintain SCRA functions, including meetings and direct and indirect assistance to GM specialty-crop developers. Of course, in the past five years, no one has obtained the funding they wanted. We don't have an IR-4-like office yet, but we will continue to give varying levels of handholding advice and encouragement to people who request it.

LANGUISHING GM SPECIALTY CROPS

We know of many GM specialty crops that have not been deregulated. We commissioned Kent Bradford and a student at UC Davis to compile a list of GM crops that were developed at land-grant universities, other universities and smaller companies. He compiled a fairly substantial list of different crops with a number of different traits that had gone through various stages of development and field evaluation and pre-commercialization trials, but then stalled because the developers were unable, for one reason or another, to continue. In some cases, the developers were misinformed and didn't approach the regulatory agencies to gain approval for commercialization. Therefore, we know that these things exist; it's not a technical problem and there may be a few IP problems, but it's largely a regulatory issue. Whether misunderstood or not, gaining deregulation is still the major stumbling block.

We wanted to contact some of these people, draw them out, and try to help them, encourage them, tell them whom they needed to talk to at the federal agencies to help them when compiling their dossiers, to tell them that they are not alone, first of all, and that successful examples are available. Ralph Scorza finally made it through with his virus-resistant plum, as the third public-sector GM specialty crop to be approved. The other two were back in the 1990s and others are currently in the pipeline, including Neal Carter's non-browning Arctic apple².

Clearly, achieving deregulation of GM specialty crops is doable. It can be frustrating, but we can provide help—admittedly in a limited capacity because we don't have a lot of funds. Hopefully, that will change in the future as the economy turns around, and we form an establishment where we can actually take particular products that need some additional trials or tests, and either commission those trials on behalf of a developer who doesn't have the in-house capability of doing them, or pair them up with people who do have the expertise, to generate essential data.

We want to encourage the commercialization of these products, because only then can we provide consumers with real choice: "Here. If you like it, buy it. And if you don't, don't."

²Pages 87–94.

ENCOURAGING ACCEPTANCE OF GM

Overcoming citrus greening is going to be interesting. I am betting that a transgenic, or at least a molecular genetic technology, is going to be part of the answer, if not the whole answer. And the disease is not confined to Florida. It's appearing in Texas and California. Similarly interesting will be tackling Pierce's disease of grapevines in California, which will also probably involve a molecular genetic technology. There's a whole range of traits that we really need to address, for which genetic technologies are the best tools in the toolbox to address them. They are not the only tools, but we have to be able to use those tools, which means that we have to overcome what appears to be public resistance. And we have to overcome misperceptions about the onerousness of our regulatory system.



ALAN MCHUGHEN is a public-sector educator, scientist and consumer advocate. After earning his doctorate at Oxford University, he worked at Yale University and the University of Saskatchewan before joining the University of California, Riverside. A molecular geneticist with an interest in crop

improvement and environmental sustainability, he helped develop US and Canadian regulations covering genetically engineered crops and foods. He served on a recent US National Academy of Sciences panel investigating the environmental effects of transgenic plants, and a second panel investigating the health effects of GM foods. He is now past president and treasurer of the International Society for Biosafety Research.

Having developed internationally approved commercial crop varieties using both conventional breeding and genetic engineering techniques, Dr. McHughen has firsthand experience with the relevant issues from both sides of the regulatory process. As an educator and consumer advocate, he helps non-scientists understand the environmental and health impacts of both modern and traditional methods of food production. His book, *Pandora's Picnic Basket; The Potential and Hazards of Genetically Modified Foods*, explodes the myths and explores the genuine risks of GM technology.

Specialty Crops and Human Health Impacts

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I am from the North Carolina Research Campus, which is devoted to nutrition, agriculture, biotechnology and functional food. Scientists from seven universities on this campus are focused on specialty crops that provide bioactive compounds, which, when you ingest them or put them on your skin topically, they interface with human therapeutic targets to counteract chronic disease or bolster metabolism to increase endurance. These are the crops that your grandmother said you should eat, and maybe you didn't because you didn't like vegetables. We are going beyond what grandma said, going beyond anecdotal evidence to try to elucidate biomarkers: what are the mechanisms of action of compounds in specialty crops that help them to interact with human therapeutic targets and counteract disease? What are these bioactive phytochemicals or "phytoactives" (Figure 1)?

Not all phytochemicals are important for human health, but phytoactives are those that bolster human health in some way, and many are present in specialty crops.

It's important to note that phytoactives are not necessarily plant nutrients. Of course, specialty crops contain nutrients as well: minerals, vitamins, *etc.*, that build strong bones and teeth. The phytoactives tend to be secondary compounds, not necessary for the plant to grow but which help human metabolism. They include pigments, anthocyanins, betalains, chlorophylls and carotenoids, which provides a convenient message for consumers: "Put some color on your plate. Don't just eat foods that are brown and white." When you do put color on your plate, you tend to be consuming phytoactive compounds, which are associated with pigments in many specialty crops. Concentrations and profiles of phytoactives vary with species and variety. Some sources are richer than others and some are more efficacious against certain disease conditions than others, but they are all there.



Figure 1. Bioactive phytochemicals—“phytoactives”—are natural compounds in fruits, vegetables, nuts and grains that positively affect human health.

At the Plants for Human Health Institute on the North Carolina Research Campus, we are investigating the gamut, from whole foods to functional foods to phytopharmaceuticals, *i.e.* removing and purifying an active compound from a plant and putting it into a pill, like a pharmaceutical. However, our major focus is on whole foods derived from specialty crops. For this presentation, I will address four questions:

- Why the Current Attention?
- How do Phytoactives Modulate Human Health?
- Can Genomics, Metabolomics, *etc.*, Pinpoint How Phytoactives Work?
- What’s the Reaction in the Marketplace?

WHY THE CURRENT ATTENTION?

You can hardly open a general-interest magazine or the popular section of a newspaper without finding something on functional foods. After Oprah Winfrey said that she “pops” blueberries like M&Ms during the day, sales of blueberries went through the roof. I talk about berries a lot because that’s my area of research, and, inevitably, the talk-show host will say, “This is wonderful, but why are we learning about it only now?” In fact, we are not just learning about it today. This is ancient stuff. Traditional ecological knowledge includes a lot on specialty crops—not named as such, of course—and their impacts on health: fruits, vegetables, spices, herbs, *etc.* The science hasn’t been behind them until now, and with the tools we have today, we are able to characterize the compounds involved. With animal models and clinical trials, we can determine how phytoactives interact in the human body, clearance times and locations of accumulation. We finally have the tools to investigate how these things are working.

To make the jump from traditional ecological knowledge to science now, it's important to realize why plants synthesize these compounds. Usually they are produced in response to environmental stress. We like to say "stressed for success" because plants, being sessile, need a cornucopia of chemical defenses against disease, insect infestation, nematode attacks, UV light, and so on. They need those defenses to survive, and they are the same compounds that, when we ingest them, counteract chronic disease.

HOW DO PHYTOACTIVES MODULATE HUMAN HEALTH?

How do phytoactives modulate human health, whether it be from a pharmaceutical, cosmeceutical or functional food standpoint? It would be advantageous if functional foods or wild plants that have phytoactive compounds acted like pharmaceuticals, with a nice bridge between using a plant to protect your health and using a pill to protect your health. But, plants don't work like that. They contain complex, interacting mixtures of compounds each of which may potentiate effects in the human body. It's hard to sort out the multiplicity of bioactivities. The compounds can do a number of different things. They might have activities against cancer and the same little group of compounds may be active also against cardiovascular disease. It's tough for doctors and scientists to understand, tending to mitigate against using specialty crops in medical treatments.

CAN 'OMICS PINPOINT HOW PHYTOACTIVES WORK?

With a pharmaceutical, you have a single active compound in a pill, facilitating dose-response and human efficacy tests. But when it's a plant extract and you tease out the components and pick out an active fraction via some activity in a bioassay, a lot of times when you purify the compound, you lose the activity. What's going on? A lot of times with plants, a synergistic effect of a potentiating compound on an active compound results in the "big bang" for human health. So there may be a multiplicity of bioactivities; blueberry is a good example. Positive effects on urinary tract infections have been attributed to blueberries—much like to cranberries—as well as beneficial effects on cardiovascular, optic, cancer and brain-function problems.

On the other hand, skepticism exists on the part of doctors, because they need to understand the biomarkers and see the proof. So, "omics" is one way to provide proof. We are starting to use genomics, transcriptomics, proteomics and, especially, metabolomics. If you have those tools in your hand, you can do a lot to decipher how active compounds are working, to pinpoint biomarkers.

We have a blueberry-genome sequencing effort that will be completed by the end of summer 2013. It's a complicated genome that no one else wanted to tackle. The database will be open to people looking at cranberry and other plants in the genus *Vaccinium*. Knowing the genomics leads to understanding activities within the human body.

The launch of the Plant Pathways Elucidation Project ("P-Squared EP") is planned for June 2013. North Carolina State and the University of North Carolina-Charlotte will be academic partners. At NC State we will handle the biology whereas Charlotte will handle bioinformatics; the biological data that we generate will go into a knowledge-based cloud over the whole project to feed information into what a plant makes, how it makes it,

what's the pathway it takes to get there, and, finally what good the product is for human health. In building this knowledge base, Dole and General Mills will be industry partners and Castle & Cooke will be a sponsor. Developed technologies will help us to understand how specialty crops contribute to human health; can we quantify it so that it's validated in every way?

General Mills and Dole have opened their files on pathways they have elucidated for oat, pineapple, and berries, and they are looking to the university researchers to pull together teams for complex pathway analyses. We will initiate the effort in two weeks, focusing on four crops with input from our industry partners: oat (*Avena sativa*), broccoli (*Brassica oleracea*), strawberry (*Fragaria x ananassa*) and blueberry (*Vaccinium* spp.). Five newly recruited PhD students will start on June 10, 2013, each of whom will supervise six undergraduate summer interns to put together pathways. Almost \$1 million have been provided by the UNC general administration to jumpstart the effort and to ensure that the PhD students will have funding for four years. It's exciting to get this going because it involves tools that we already had but we needed manpower to put them to work to generate useful data. Several local junior colleges and schools in the UNC system are donating interns. We will not donate any, but we will pay the interns to work intensively with the PhD students as teams.

Clinical Trials

Another example of how we get to the bottom of how specialty crops work is with clinical trials. These have always been horribly expensive, which is why they have not been used to investigate specialty crops or functional foods. We are fortunate to be partnering with the Appalachian State University and members of their human performance laboratory where they do clinicals, many with athletes—runners, cyclists, NASCAR pit crews, *etc.*—looking at the effects of functional-food components on exercise performance. For example we have done some work with runners, supplementing their diets with blueberries and green tea to see the effects of polyphenolics on classic markers of inflammation and oxidative stress using metabolomics. Classically you don't see oxidative stress or inflammation changes in highly trained athletes, but a nice thing about athletes is that they will cooperate if they think that the process will improve their performance and make them stronger. You don't have to pay them as much as for a normal clinical trial and they permit biopsies.

After consuming a supplement of blueberry green tea for 14 days, athletes were exposed to periods of intensive exercise, sufficient to induce oxidative stress (Figure 2). Only insignificant differences between the placebo and treatment groups were seen in the gross markers of oxidative stress like C-reactive protein. But we did see differences in bioavailability. The athletes who were supplemented had excellent profiles of gut bacteria metabolism of phenolic phytochemicals. We saw, for the first time, that compounds from blueberry and green tea were actually getting into the blood of the athletes, intensified by kind of a gut leakiness with intensive exercise which persisted during the recovery period, so that bioavailability was intensified as revealed by the polyphenolic signature. Gut microbial metabolism of the plant polyphenols was clear in the treatment group versus the placebo group. Furthermore, runners who were supplemented with blueberry

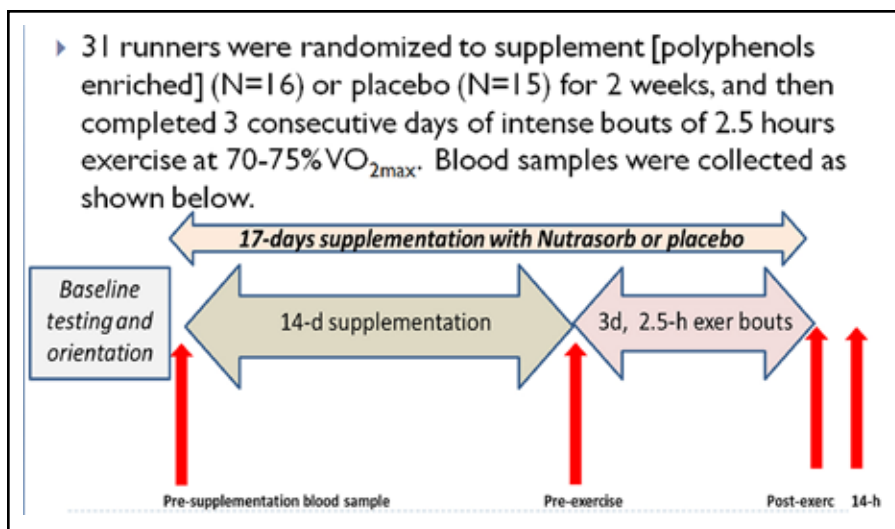


Figure 2. What are the effects of phytoactives on athletic performance?

green tea protein continued to utilize fatty acids—they had higher ketogenesis—during the recovery period. Athletes show a burst in oxidative stress and fat burning while they are exercising, but, whereas the placebo group went down to normal levels during the 14-hour recovery period, fat burning continued in the treatment group, which was quantifiable using metabolomics.

REACTION IN THE MARKETPLACE

Wild blueberries have been harvested commercially for many years in Maine and the maritime provinces of Canada; it's backbreaking work (Figure 3). Although it was the second largest industry in Maine, it was not highly lucrative for farmers until, in 1998, the “antioxidant” message emerged (Figure 4).

This wild blueberry antioxidant message was confirmed by researchers in Canada and the United States, and later in Europe. A lot of work has been done on wild blueberries and diabetes and obesity. Data from clinical trials at the Pennington Biomedical Research Center are conclusive for efficacy of blueberries for increasing satiety in their patients and cutting triglyceride levels. For hyperglycemia—the hallmark of diabetes—wild blueberries did better than metformin, the drug of choice for diabetes; blood-glucose levels were reduced in six hours. These and similar data attracted much media attention.

In 1999, colleagues at Tufts University, Barbara Shukett-Hale and James Joseph, showed that inclusion of blueberries at 2 percent of the diet alleviated or prevented the symptoms of dementia in artificially aged rats. Furthermore, losses in cognitive and motor function were partially replenished by introduction of the blueberry diet. This and similar research, reported in the mass media, have taken the humble blueberry from an addition to muf-



Figure 3. Labor-intensive harvesting of wild blueberries in Maine.

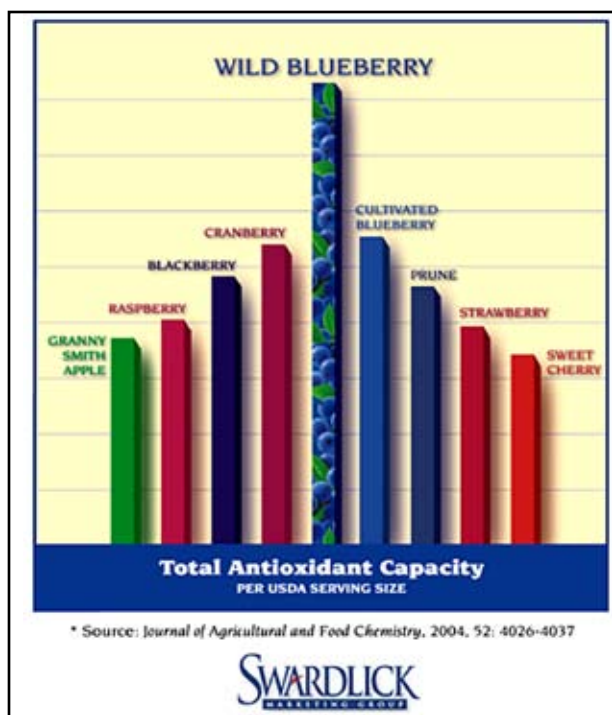


Figure 4. Nature's #1 antioxidant fruit.

finds to a health icon. These days, it's hard to pick up a health-related magazine without finding something about blueberries in particular. Other functional foods from specialty crops have benefitted in the same way, because people are turned on to what they can do proactively for their health.

Figure 5 shows increased production of cultivated and wild blueberries since 1998 when news of positive health effects first made the headlines.

We know what we're supposed to eat and we know how much we're supposed to eat. However, it's estimated that approximately 1 percent of the American public—including educated people—actually eats the amount of fruits and vegetables they're supposed to eat. There are many reasons why people don't do what they're supposed to do. How do we take bioactives from fruits and vegetables, from specialty crops, and get them in a shelf-stable, convenient form to more people?

We are working with the US Army to develop ways of getting fruits and vegetables to soldiers in the field. Figure 6 shows shelf-stable, low-sugar protein-rich flours containing extract from muscadine grapes. The same can be done with kale extract. The preparations are stable for over three years in some cases. Soldiers in the field will eat it because it tastes good, it's nutty, and they don't care if it's GMO or not.

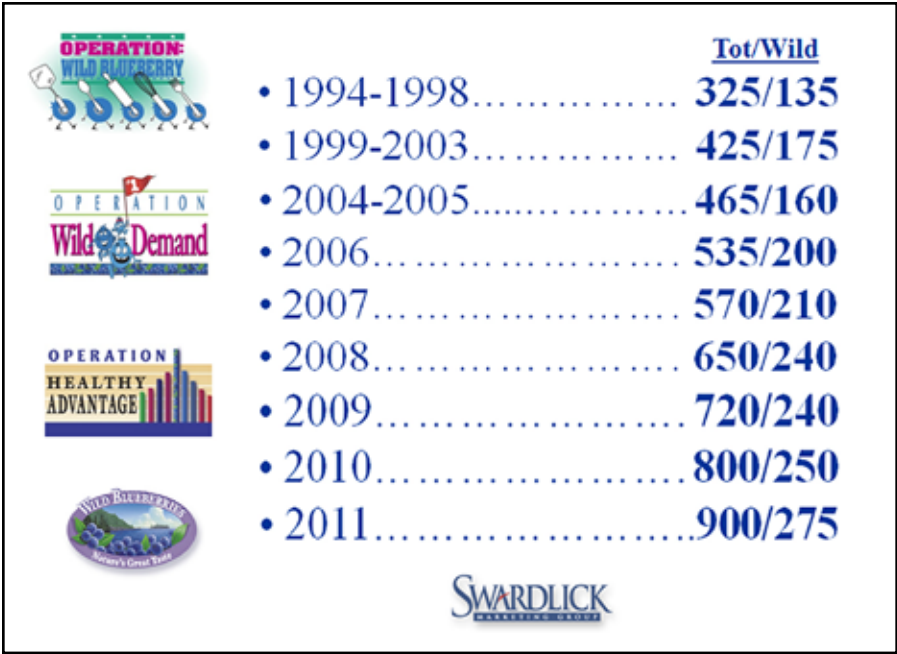


Figure 5. Blueberry production trend ($\times 10^6$ pounds/year).

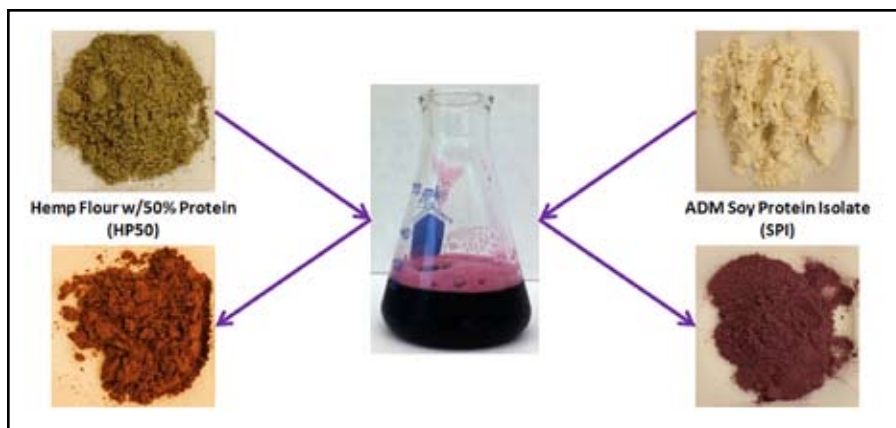


Figure 6. One-step sorption of the medium polarity polyphenolics in muscadine juice, free of unwanted/non-nutritional material.



MARY ANN LILA is director of the Plants for Human Health Institute (PHHI) at North Carolina State University on the NC Research Campus. She holds the endowed David H. Murdock chair, and is a professor in the Department of Food, Bioprocessing, and Nutrition Sciences. Through transdisciplinary discovery and outreach, the team at the PHHI is pioneering a dramatic shift in the way the American public views and uses food crops, not merely as a source of nutrients and flavorful calories, but as sources of powerful components that protect and enhance human health. Her research team focuses on wild and domesticated berries and their wide-ranging health benefits, including alleviation of the symptoms of diabetes and metabolic syndrome. Current efforts include a Bill & Melinda Gates Foundation Grand Exploration Challenges project in Zambia and projects in Egypt, Central Asia, Oceania, Mexico, Ecuador, Chile, subSaharan Africa and New Zealand.

Formerly (2006–2008), she was director of ACES Global Connect (the international arm of the College of Agriculture, Consumer and Environmental Sciences at the University of Illinois) and associate director of the Functional Foods for Health Program (1997–2000) at the University of Illinois. She is vice president of the Global Institute for BioExploration, an R&D network that promotes ethical, natural product-based pharmacological bioexploration to benefit human health and the environment in developing countries.

Transforming Modern Agriculture Through Synthetic Genomics

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In this talk, I will cover a few topics. First, I will describe some of the cutting-edge science that's underway and how we are applying it within Synthetic Genomics, not specifically on specialty crops as defined, but on low-acreage or potential crops of the future. Many of these concepts will apply to specialty crops.

We can think about progress in synthetic biology, much in the way that children progress through school (Figure 1). First, in 1995, whole-genome sequences were published for two simple bacterial species (*Haemophilus influenzae* and *Mycoplasma genitalium*), which, in the late 1990s, were followed by publication of several plant genomes, culminating in 2001 with the publication of the draft sequence of the human genome. That was equivalent to learning to read, as in early grade school, begging the question: "If we can read the genetic code, can we begin to write it?" In 2003, the synthesis of a small viral genome was achieved, at a little over 5,000 base pairs. In 2006, effort was initiated to chemically synthesize a bacterial cell. The result was published by J. Craig Venter Institute researchers in 2010: fundamentally, this organism came from nature and we recapitulated it with a few additional sequences.

WRITING STORIES

What's important now is to take the tools that we have developed in reading and writing to create our own stories. This is where the design aspect gets interesting in terms of developing crops that not only are more robust and higher yielding, but can be more beneficial from a health standpoint. Focusing on some of the tools, Figure 2 shows a simplified diagram of the process used to produce the first chemically synthesized cell, which has a genome of about 1.1 megabases, *i.e.* over a million base pairs. When this

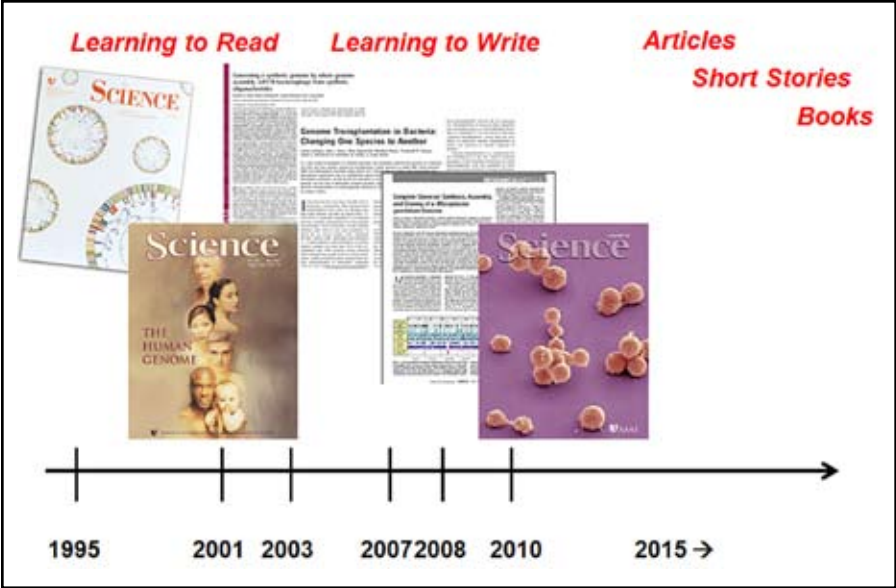


Figure 1. Progress in synthetic biology.

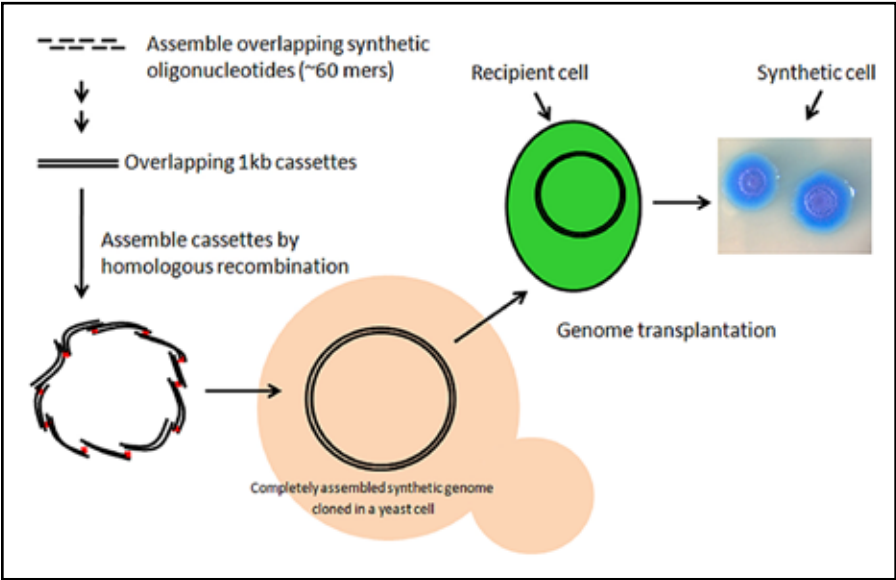


Figure 2. Approach used to synthesize a *Mycoplasma mycoides* cell.

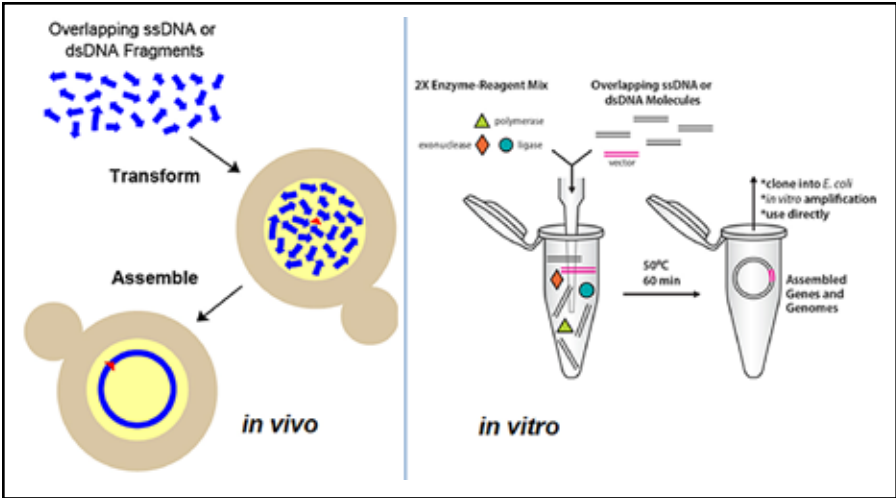
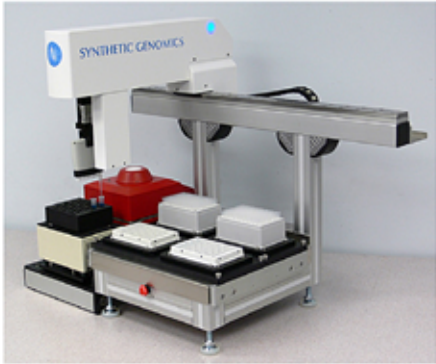


Figure 3. DNA synthesis/assembly methods: alternatives enabling combinatorial assembly.

Oligo Pools → Biological entities (DNA, proteins, viruses, and microbial cells)

produces 1 – 32 genes every 8 hours



- * SGI-Third Party relationship
- * Includes SGI proprietary DNA synthesis and error correction methods
- * Progress is monitored through email
- * Received at SGI in December, 2012
- * dependable: synthesis of 24 1.5kb constructs in a single run and >3kb fragments per run

MAX CAPACITY (bp/instrument)

Daily: ~190 kb	Monthly: 5.8 Mb
Weekly: 1.3 Mb	Annual: 70 Mb

Figure 4. Automation of DNA assembly.

project was undertaken, the largest DNA assemblies that had been produced were of about 30 kilobases—about a thirty-fifth the size. One of the challenges was stitching DNA together accurately in these large assemblies. Several methods were developed, but constructing these assemblies was only part of the problem; the next question was how to activate it and give it life. Methods were developed for handling whole genomes and transplanting them into related recipient cells that essentially served as the birthplace for the new genome. And again, in this case, much like a virus takes over the host cell, the transplanted genome was replicated, transcribed and translated, producing marked synthetic cells as in Figure 2.

SIMPLE METHODS FOR DNA ASSEMBLY

Important for future progress was the development of some simple, but powerful, methods for assembling DNA. The right-hand side of Figure 3 illustrates the Gibson assembly method, now utilized in many laboratories; Dan Gibson's insight was to use DNA-repair mechanisms as the basis for developing an *in vitro* mix that is isothermal and reliable. This method is quite amenable to automation because of its relative simplicity, and Figure 4 shows a unit we received in December of 2012, the prototype of a benchtop instrument that will allow all laboratories to synthesize genes or even larger segments of DNA.

The instrument is loaded with the oligonucleotides encoding the gene of interest, a button is pushed and overnight the constructs are made. And this has actually been used for rapid production of influenza vaccines. SGI has a number of partnerships with leading companies, including Novartis Vaccines to develop a faster method to synthesize vaccine seeds so that Novartis can get a supply of influenza vaccine to the market more rapidly. The importance of this was illustrated in 2009, when the H1N1 epidemic was of great concern. As Figure 5 shows, the number of cases was growing exponentially before the vaccine became available. The reason it took so long to get the vaccine to market was both a function of a long process to develop the vaccine seeds as well as low yields with the H1N1 virus.

There needed to be a better solution, so the Centers For Disease Control Board/ Biomedical Advanced Research and Development Authority (CDC/BARDA) is funding Novartis and Synthetic Genomics to develop a better, faster and more reliable method for, not only producing vaccines for seasonal flu cases, but also to have a method that can be used for responses to pandemics. We have been successful in taking what is typically a six-week process using classical genetics to isolate virus-vaccine seeds to a process where, now, when the World Health Organization releases information about a strain, we take that sequence and, using our assembly methods, can synthesize the DNA constructs in about twelve hours, achieve infection of mammalian cells and recover active virus seeds in five to six days. This shortens the process by about six weeks. In the long-term, we will be able to survey all of the possible materials out there and bank the viral gene segments for assembly overnight when called for. This was recently reported with the H7N9 strain in China, which is currently not available in the United States. However, BARDA requested it and we were successful in assembling and producing a vaccine seed without having those viral strains available.

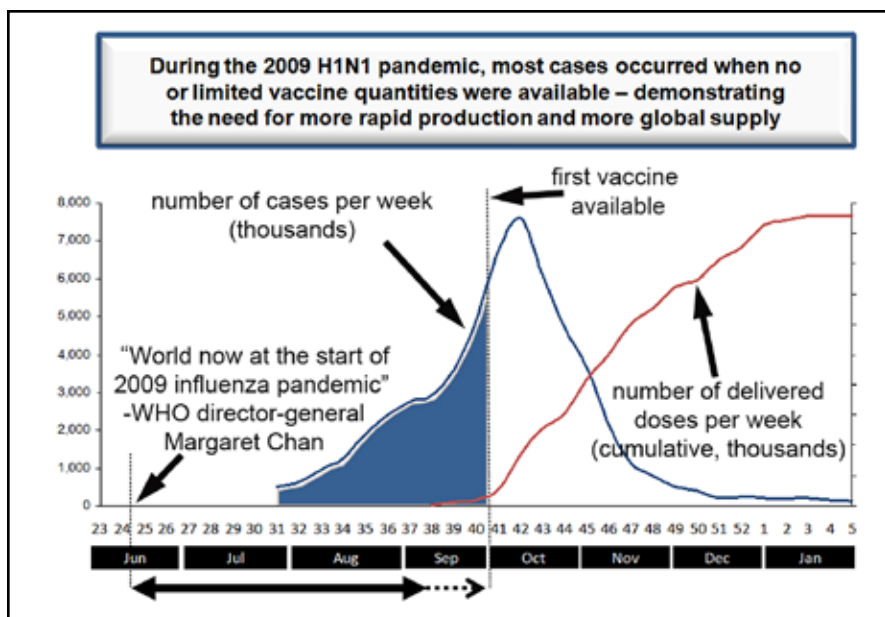


Figure 5. Synthetic Genomics case study: Influenza vaccine.
 (Data provided by Phil Dormitzer at Novartis Vaccines & Diagnostics.
http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm)

These improvements in speed are important, but so too is accuracy. We have worked hard to develop methods to weed out errors that are inherent with oligonucleotides, the 60-base-pair segments that are the building blocks for genes and, ultimately, genomes. They can be only 60 percent to 70 percent pure, therefore, if large numbers are stitched together, assembly errors are almost guaranteed, which can be problematic. To address this, we have used bioinformatic capability to develop error-correction methods that we now incorporate routinely. This allows us to accurately assemble DNA segments of up to seven kilobases without intermediate sequencing to verify accuracy.

Another important factor is cost. At the time, building the genome of *Mycoplasma mycoides* cost about \$1 million in reagents alone. It was a fascinating project, but not something that would be taken on routinely because of the necessary expenditures. This field as a whole depends not only on improved accuracy, but on lowering the cost of DNA assembly. Figure 6 shows the exponential decrease that has occurred in sequencing costs since 1990, which has fostered applications of “omics” technologies.

We haven’t seen the same reduction in cost of gene synthesis (Figure 6). We and scientists in several other labs are working on methods that involve ultra-low-cost DNA sources from microchips as well as next-generation sequencers that allow retrieval of validated correct sequences to begin assemblies. If successful, these methods could lower the cost by at least an order of magnitude, bringing the assembly cost down to a penny or two per base, presenting the possibility of new ways of improving specialty and other crops.

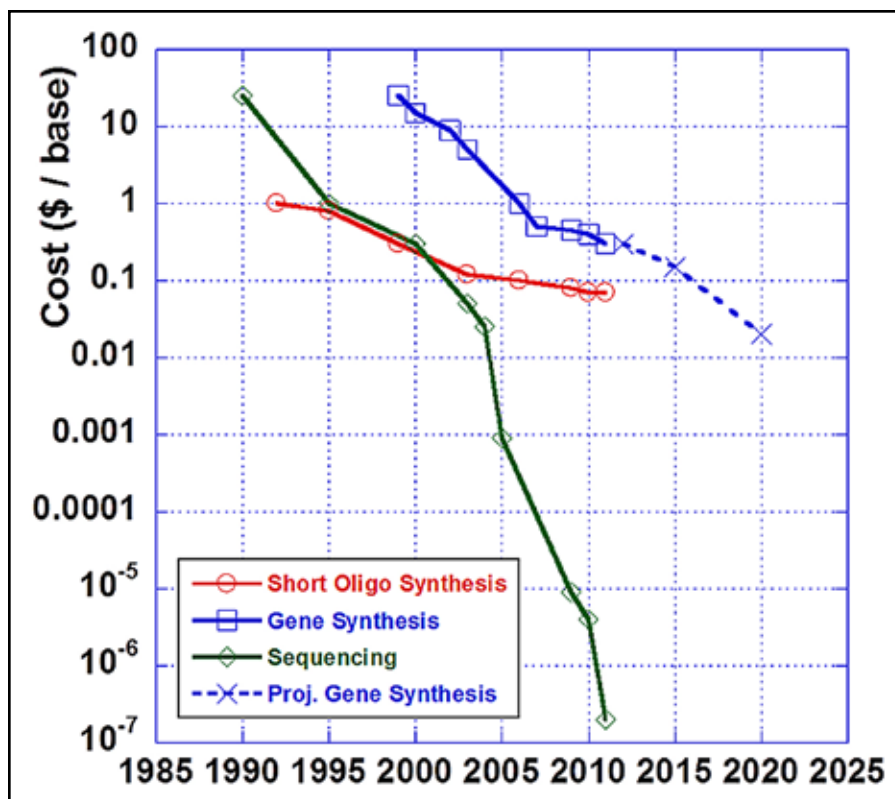


Figure 6. Cost trends: DNA synthesis and assembly.
(Adapted from R. Carlson, www.synthesis.cc.
Includes SGI Projection.)

TRAIT DISCOVERY AND PATHWAY ENGINEERING

Over the past six years, we have developed a web-based scalable comprehensive bioinformatics platform to allow not only computational biologists, but also novice users, to analyze genomic information and to use that information in design and construction of DNA assemblies for recombinant cells. And we have done an extensive amount of biodiscovery and characterization of fungal, plant and algal genomes, which increases the diversity of information available for our work.

Using our proprietary enrichment and isolation methods, we have acquired some 4,000 microbial isolates—associated with wild grasses—that have been screened for various properties. One of the interesting things that came out of this was the idea that, with these bioinformatics methods and knowledge of gene structure/function, we could then use bioinformatics as an assay in the discovery effort. With a view to discovering new *Bt*-type insecticidal toxins, we took our *Bacillus* isolates—a subset of about 200 in

- 188 mutants of enzyme A created (two plates)
 - alignment with enzyme B and crystal structure analysis
 - 1 - 43 aa were mutated
- 110⁺ mutants folded properly (absorbance assay)
- Screened reactivity against substrates 1 and 2
 - native enzyme A has no reactivity with either substrate
 - engineered enzyme A products obtained with both substrates
 - >10 mutants showed products from a target substrate

Figure 7. Engineered enzyme activity results: the substrate range of the target enzyme was modified creating the desired activity.

number—and isolated the plasmid DNA potentially encoding such toxins, pooled those plasmids, went through a next-generation sequencing effort and then were able to assemble and annotate that information. Within a six-week period, we discovered fifty full-length novel *Bt* genes. This pilot test demonstrated the potential utility of this extensive amount of information when analyzed with the new tools.

We now have the ability to efficiently and cost-effectively assemble DNA structures from starting-material oligonucleotides. We can now construct digitally designed protein variants rather than employ traditional methods that involve either random changes such as error-prone PCR or gene shuffling or site-directed mutagenesis, which allows us to make base-pair nucleotide changes, but only in specific regions. Being able to design this on the computer gives us unlimited flexibility.

We had an enzyme for which we were trying to modify the substrate specificity to induce a desired carbon-carbon bond-cleavage reaction. We had an enzyme that performed other chemistry on those identical substrates and then we had “enzyme A,” which in fact did not work on those substrates but catalyzed the reaction of interest. Through protein modeling, we identified a number of changes that would be beneficial within and outside the active site and made a set of 188 protein variants, which we screened for function (Figure 7). Within one round, we obtained ten mutants that worked on both of the substrates of interest. In essence, we had engineered the desired change in substrate specificity.

MOLECULAR BREEDING FOR SPECIALTY CROPS

One of the foci of our AgraCast subsidiary is the development of castor-oil plant (*Ricinus communis*) as a source of specialty chemicals. Castor is of interest due to its high content

of ricinoleic acid, a hydroxylated fatty acid that provides a platform for producing branch-chain chemicals. It is used by BASF to produce lubricants, for example. However, a barrier to broader scale adoption is lack of availability, lack of consistency and high cost. Although it grows wild in Texas and in Mexico, commercial production is mainly in India by small farmers with relatively low yields, one to two tons per hectare. Typically, it is harvested manually because of the plant's architecture. Several years ago, we began both classical and molecular breeding programs to identify plants with larger racemes and higher yields (Figure 8). We are up to about four tons per hectare.

ALGAE AS A MAJOR CROP OF THE FUTURE

By FAO estimates, we will need to increase the food supply significantly in the foreseeable future, and we will have to do it without accessing more arable land, usage of which has been stagnant for decades. That, coupled with issues associated with climate change, increasingly important issues around water availability and the fact that we are seeing increases in demand for animal protein that are primarily correlated with increased economic development, we see the need not only for increased productivity of our major crops, but also of new crops that can be cultivated on non-arable lands with minimal inputs of fresh water.

We have had a collaboration with Exxon-Mobil since 2009, researching algae for use as biofuels, but we may see this commercially utilizable in production of algal-based proteins. The potential is shown in Figure 9: algae—even the current forms—are much more efficient producers of protein than are terrestrial counterparts. Our characterizations show that algal protein provides complete sources of amino acids and are highly digestible. Major barriers associated with algae as commercial sources of protein include developing domesticated species that will grow robustly in the wild. We see a need to use synthetic genomics techniques to combine beneficial traits that have utility under specialized conditions and combine them with photosynthetic efficiency, to allow us to channel carbon to target molecules and show improved tolerance of environmental stresses. One of the most significant things that we'll be reporting on towards the end of 2013 is research to improve photosynthetic efficiency.

Figure 10 shows that when algae grow in dense culture, light becomes limiting and overall productivity decreases. In part, this is because, when light is low the algae acclimate and build larger antennae that shade their neighbors. We have engineered semisynthetic algae that are deregulated in their response to light, allowing significantly more light to penetrate the culture without compromising the photosynthetic processes and functionality of the cell. We've also taken similar steps to increase lipid productivity in just a matter of a few months, again based on bioinformatics and our ability to modify biosynthetic pathways. Our algal research is at an early stage, but our synthetic genomics techniques give the ability to accelerate the developmental process. Ultimately, I think that we will see large-scale algal-production facilities providing a growing share of protein requirement in the future.

<u>Why Molecular Breeding?</u>	<u>Molecular Breeding Targets</u>
<ul style="list-style-type: none"> • Faster crop improvement • Reduced phenotyping costs • More rapid hybrid development • Quality control • Protect IP (Elite Lines) 	<ul style="list-style-type: none"> • Plant size • Proportion of female flowers • Raceme size • Disease resistance • Toxin elimination
<hr/> Molecular breeding will sustain Agracast competitive advantage in castor <hr/>	

Figure 8. Molecular-breeding rationale and targets: the molecular-breeding approach developed for large-acreage crops will be increasingly applied to specialty crops like castor bean.

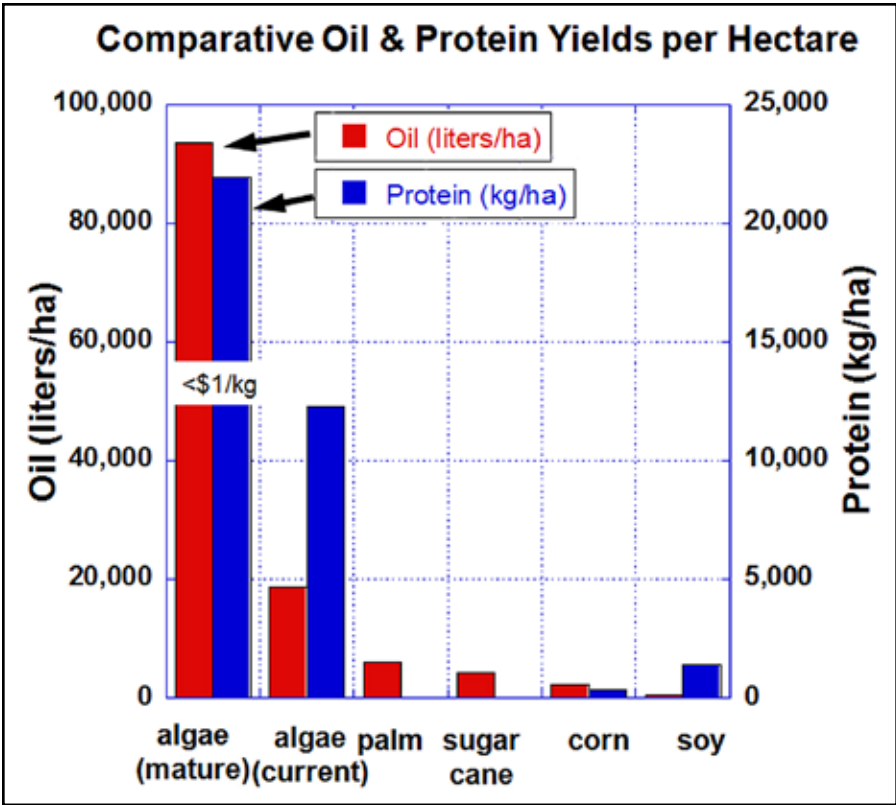


Figure 9. Algae is the best, scalable production system in a land-, water-, and carbon-constrained world (data based on various literature reports).

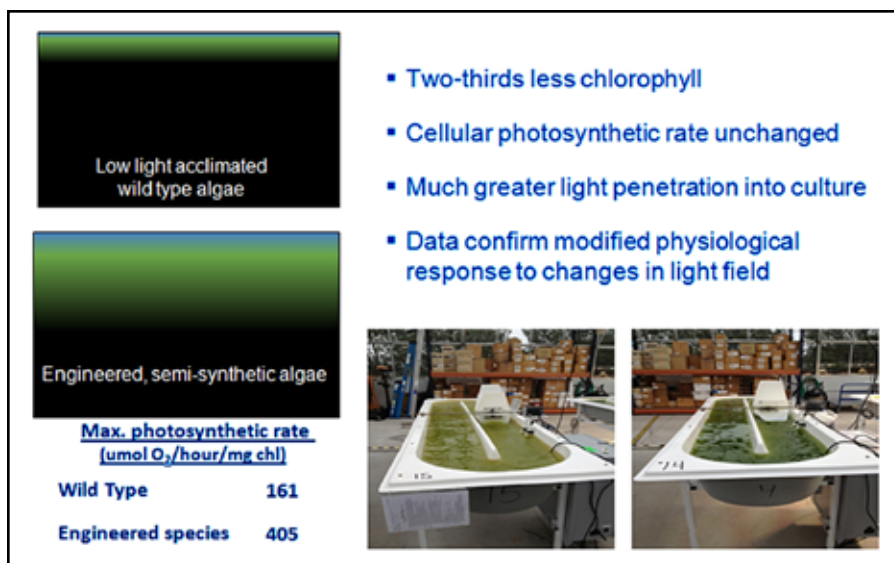


Figure 10. Engineering algae for improved photosynthetic efficiency: increased light penetration and improved photosynthetic efficiency.



JIM FLATT is the chief technology officer at Synthetic Genomics, Inc., a leader in the development and application of synthetic biology for sustainable production of fuels and chemicals and applications in agriculture. He has been involved in the industrial biotechnology field for over 20 years. Prior to SGI,

he was the executive vice president of research and development and operations at Mascoma Corporation, a leader in the development of cellulosic biofuels. Before joining Mascoma, he served as senior vice president of research for Martek Biosciences Corporation, leading the development of nutritional fatty acids from microalgae that are now included in many infant-formulas and other food products. And prior to Martek, he was involved in microbial biotechnology research at Merck and Monsanto.

Dr. Flatt received his undergraduate degree in chemical engineering from Massachusetts Institute of Technology and graduate degrees in chemical engineering from the University of California-Berkeley and University of Wisconsin-Madison. He has served as chair of the industrial advisory board for the National Science Foundation Engineering Research Center for Marine Biotechnology at the Universities of Hawaii and California-Berkeley.

Session 4: Perspectives from Relevant Groups

Q&A

MODERATOR: DANIEL LESKOVAR

Texas A&M University

College Station, Texas

Scott Thenell (Thenell & Associates, Walnut Creek): Tom, earlier you asked about identity preservation¹ and whether I thought that would work. Obviously, the Soybean Association has identity preservation; can you give us an idea about the additional costs?

Thomas Redick: They have what they call the eleven-point plan for keeping things separate in soybeans. Soybeans are self-pollinating, but there are all kinds of opportunities to commingle in the chain. The premium for that is a negotiated element, so additional costs you incur depend on your own farm, whether you have a guild, and so on. Maybe you are growing white corn for FritoLay and are part of a network contributing to a dedicated elevator. So, \$.40 a bushel is just one example. It could be more, it could be less. Definitely, if you are going to go to a specialty preserved chain of commerce, the costs of identity preservation mean that the grower is not going to do it unless there is something in it for him. It could be a 10-year contract that he's guaranteed. That could do it, if you have a guarantee that every year they are going to buy what you grow. But, usually, you need something per bushel to sweeten the pot before you are going to agree to a fully identity-preserved production system.

¹Page 218.

Ralph Hardy (National Agricultural Biotechnology Council, Ithaca): In the pesticide area they have special exceptions for certain crops, called IR-4. It's also my recollection that there is some harmonization between the Canadians and the United States in IR 4. Does that concept have any relevance to any of these specialty crops we are talking about?

Redick: Yes. When we did the Accord, we first talked to folks involved in IR-4 because they have their own data-compensation system with USDA oversight. That was designed mainly for specialty crops to ensure they get the active ingredients they need when they go generic. So, that was driven by a need for chemicals to go into the right places where they are needed—whether they are generic or not—without worrying about overseas approvals and data and whether issues have been resolved. So, there are plenty of models to be followed, and the Accord will be filed this summer. I think the final steps will be done and we'll have a document that folks in the specialty sector may also use for patents that have expired.

Roger Beachy (Global Institute for Food Security, Saskatoon): Are there any opportunities for North American identity preservation that would ease some of this? Are there products that could be from Mexico, the United States and Canada that that could be called out, without need to worry so much about other exports to other countries?

Redick: I think you could produce a crop in a closed-loop and assure the stakeholders who matter that this has been produced in a closed loop, not commingling with the export chain of commerce. The trick is going to be to find the place to grow it, where it's not going to just automatically—

Beachy: But are there products that have enough market to do that?

Redick: A high-oleic soybean that came out in 1999 was grown in a closed-loop but never made the market because of the cost. So, there's no guarantee that the identity-preservation cost will justify the new event that you are introducing in a specialty crop. In the soybean sector at least, everything has been grown for major market approval. In corn, they only have two markets they care about. So their board has voted only Canada and Japan, not even Mexico. And Mexico has actually allowed that because they eat so much of our corn and feed so much of it to their animals. So, it's possible that carrots could be more like corn than like soybean. Maybe there's not a big export market for certain crops. Maybe there are governing stakeholder groups that say, "We want the innovation." There are models out there for doing it with just a couple of key markets.

Beachy: Then I have one more. Has there been sufficient validation from the market on the heart-healthy oils? Will consumers pay more for them? I just don't know how that consumer research is going. And does that pay for segregation?

Redick: That's the great untested question. There are issues too like glycosylation of omega-3s. CAST has actually written a paper on that question. So there's a lot of tough science before you're going to find on these specialized oils meeting scientific nutritional equivalents. I don't know that every one of those is guaranteed. Actually I've heard people say that a third of those might actually find the market. Soybean oil economists project that you really have to meet certain levels of marketability to get in the niche. But the high-oleic soybean that is coming out now—they are looking at 25 percent to 50 percent of the market share because it can fry fast food better and deliver a heart-healthy benefit—called Plenish® and other names. They think they are going to get a good market share. The soybean check-off is putting a lot of money into making that happen, so we'll see if the market accepts it.

Allan Eaglesham (NABC, Ithaca): Mary Ann, are wild blueberries more effective than cultivated blueberries and, if so, do you know why?

Mary Ann Lila: Yes, because they are more concentrated they withstanding more stresses. In some ways it's like the organic vs. non-organic argument. But yes, plants in the wild accumulate more phytoactives.

Bolormaa Jamiyansuren (University of Minnesota, Minneapolis-St. Paul): Dr. McHughen, you mentioned that people who were against GMOs do purchase GM products after seeing the price. I am gathering information on GM products in terms of being cheaper or more expensive than conventional or organic products. Can you give a reference to that? Or did you do a study on that?

Alan McHughen: The studies have not been properly done, or at least not for several years. In some of the early academic studies prices were equal so consumers making a GMO/non-GMO choice didn't have price as a consideration. We need to do more of that and have prices reflect what consumers will see in the marketplace. Presumably, if the GMO has a benefit to it, at least agronomically, the price should be lower because of the increased efficiency of production. Of course, this will also help to sell more of the product. At least for those people who have an open mind, if they see good quality at a lower price then they will be inclined to purchase. We did see this early on in the UK when GM tomato paste was on sale for a short time. Unfortunately, the cans of tomato paste were of different sizes so even though the genetically engineered tomato paste had a lower price, consumers couldn't make a direct comparison. But the GM paste was less expensive and, apparently, that is what many consumers chose to purchase. But we will be able to answer this only when we have multiple products in multiple markets and really see how the consumers treat them. But I'm convinced that the vast majority of people don't particularly care how the product was made as long as the price is good and the quality is good.

Jamiyansuren: Dr. Lila, you convinced us that blueberries are very good. In terms of the blueberries and green tea, your slides indicated statistically significant improvement in the treatment group compared to the control group. I wonder about a human factor; if a very healthy man happens to be in the treatment group might it produce a better result than with the control group?

Lila: They were all high-performance athletes across the board. I was working with ASU, using their standard experimental design—all high-performance athletes.

Bill McCutchen (Texas AgriLife, College Station): Jim, can you tell us the exact date on which we will be able to use the technology you were talking about—homologous recombination—to make changes in specialty crops without going through regulatory processing? A little joking, but how far away are we from being able to make those types of changes?

Jim Flatt: Most of my insights in this case are gleaned from our work in algae as really simple plants and plant models. We have been successful in developing HR homologous recombination methods for several of the algae. But, I can say that this is very species-specific and has required a lot of work to get there. I do think it's possible, although efficiencies vary among the couple of species that we have used to develop the genetic tools. One of the things that is beneficial here, though, is in terms of developing some of the nucleases to make double-stranded cuts in DNA. We have benefited in our work from the ability to make these very specific modifications, in trying to improve the efficiency of that process. I wish I could give you the exact date; it's probably still several years off. Certainly, we see some glimmers of hope at least from our work.

McCutchen: Do you see the possibility, using viral vectors for delivery within the plant for homologous recombination? In other words using that as a carrier or other symbionts?

Flatt: Sure. If we can deliver the DNA or RNA we're usually able to get good expression. Irrespective of the method of delivery, if we have the right sequences we should be able to ultimately make the desired changes. But, we've not specifically worked with viral vectors so I can't speak any more definitively on that.

McHughen: This illustrates an important concept that we haven't really discussed: developing methodology to circumvent regulations and this is a problem when your regulations are triggered by process rather than product. Lots of new technologies have been developed since the dawn of recombinant technologies and some of those may be captured by current wording in the regulations and some of them may not. But, really, the question is whether our environment and our society adequately are protected from real threats to our health and to our environment. We can't achieve that based on a process trigger because we are always going to be playing catch up. When harm is caused, it is due to the presence of products. So, let's change our regulation so that they are product-triggered and not have

to worry about work-arounds or companies that may be interested in trying to invest in a way to avoid regulations. I'm in favor of sensible regulations—not no regulations.

Beachy: First, I endorse what you just said Alan. I'm curious as to how we take the information that you gave us, Mary Ann, about benefit and validation of beneficial attributes of horticultural specialty crops, and then using that to amplify, through synthetic biology, metabolic engineering, to enhance specialty crops. A number of us have worked in that space. At the end of the day though, the consumer needs to pay more. How far off are we before consumers will actually pay for a beneficial attribute? A lot of people have spent money in this space, even analyzing consumer attitudes and found out they want more but don't want to pay for it. Jim, how does that affect what you decide to do in the company, because it's all costed by likelihood? Do you delay certain things for the next five years until attitudes change? How do you see this moving forward to really have good products?

Lila: We've been talking through this whole conference about regulation holding things back and in the case of specialty crops and health you almost wish there was more regulation on what the media say and what they put out there. People who have serious problems with health or suspect or are paranoid about that, will pay. They will pay extra for something that is validated. Maybe they don't understand the science, but if they feel it is validated and substantiated you will get the extra premium. I can't put a number on it.

Flatt: Yes Roger, that is a great question and I'll address it in a couple of respects. When we embarked several years ago on our food efforts, we actually spoke with a number of very large multinational, both commodity as well as consumer packaged, food companies and a couple of things that those discussions bore out—the first is that the more visionary companies definitely saw that there would be growing acceptance of these methodologies in particular if they provide benefits that consumers can recognize. I think this is the point Mary Ann was making. So, again, to the extent that there is a validated clinically proven health benefit or a reduction-of-risk benefit or a performance nutrition benefit, there is certainly abundant evidence that consumers will pay for that, and oftentimes it is less important how that is produced. Having said that though, companies are very sensitive with their image and perception and have asked us to, as we are developing our products, to be able to provide them in two forms if you will have it, one that will essentially allow them to provide choice to their customers as well as deal with regional worldwide sensitivity. So, in some markets it's acceptable to produce that product through a GMO whereas in other markets you are still looking at identity-preserved sources. One of the things that we have been working on is how we can do bioinformed sorts of classical strain or cell-line improvement. And so we've had some progress there but, of course, you are still limited in the complexity of problems you undertake. We guide our product development making sure we can meet both of those needs. Because, again, you can't bet the whole farm—especially if it's a smaller development stage company—on producing a technical success but a market failure.

Ralph Hardy (NABC, Ithaca): At NABC 22, at the University of California, Davis, there was discussion of what was adequate proof of efficacy of some of these entities. One of the examples that was used was Activia yogurt. The European scene has required an efficacy hoop that is almost impossible, as I understand it, to exceed. That barrier is: it has to be proven the same as a drug. What guidance would you give in terms criteria to be used in the United States and Canada to be appropriate demonstrations of efficacy?

Lila: Hard to say, but definitely moving to the clinicals is the important thing, which they are doing more and more now. We had such a long drought of just cell-culture studies, which—I'm not downing those—certainly get to some answers, but they don't get to the answers that you really need to make a claim. Even when you do have validated repeated clinicals, you still have regulatory hurdles to pass through. But I think that clinicals—clinical trials—have to be the gold standard to validate a product or a technology.

Flatt: Mary Ann, in a prior life you were involved in a lot of nutritional research and one of the barriers in doing good research was just really the limited amount of money and the large base size for a clinical population. One of the trends that we have seen, in speaking with various nutritional researchers around the country, is using bioinformatics to carefully select and screen the test population so that you can get very meaningful data from a much smaller sample set, which helps get you a much more homogeneous test population with fewer subjects and allows you to draw definitive, statistically valid conclusions. I think that is something that we will see growing and hopefully will help.

Beachy: When you make those selections of population you do it for a variety of reasons; do you include microbiome in those populations that eventually would be your test case?

Lila: Because it's becoming more and more—

Beachy: It makes your selection of who that test case is more expensive to evaluate.

Lila: It does, but individualized nutrition is part of it, and what works on one population will not work on another.

PART IV—STUDENT VOICE AT NABC 25

Student Voice Report

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*Matthew Bernard, Parisa Fallahi, Bolormaa Jamiyansuren
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*Student Voice Report*¹

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Each year, the North American Agricultural Biotechnology Council (NABC) holds a conference as a platform for all stakeholders of biotechnology in North America to discuss immediate issues. For 2013 (NABC 25), the theme was *Biotechnology and North American Specialty Crops: Linking Research, Regulation and Stakeholders* and bringing smaller-scale genetically-modified (GM) crops to market despite challenges of policy and perception. The NABC reserves a portion of the conference, the *Student Voice*, for students to offer their insight.

The *Student Voice* program was inaugurated at NABC 19 in 2007 to promote graduate student participation in NABC. A single representative from each member institution is sponsored by the NABC with a travel grant of up to \$750 to cover travel costs and lodging at the meeting with the conference registration waived. The student representatives attend all of the plenary sessions, the breakout session, and meet separately to develop key points of interest that were presented at the conference. The following are the issues and concerns deemed important by the NABC-25 *Student Voice* representatives.

POTENTIAL PROBLEMS FOR THE FUTURE AND SOLUTIONS

Our concerns for the future fall into three general categories: Communication, Education and Funding.

¹All authors contributed equally.

Communication

There is a lack of interdisciplinary collaboration and communication outside of the life sciences. Life scientists do not consistently collaborate with sociologists, economists, or marketing experts, whereas, in industry, such collaboration is standard. Increasing interdisciplinary cooperation could lead to improved public perception of genetically modified organisms (GMOs).

Also important is communication between scientists and the general public. There is a preference on the part of the public to be informed by arbitrary events and opinions of celebrities—frequently disseminated as “tweets”—rather than by scientifically substantiated discoveries. Although many celebrities do not necessarily speak out against GMOs, they may lobby in favor of labeling GM foods/ingredients. An ongoing campaign (justlabelit.org, 2012) is advocating a petition to oblige the FDA to enforce mandatory labeling of all GM foods. Interestingly, the *Just Label It* campaign is organized by a self-titled group called the *Organic Voices* whose major partners are organic producers, and, what is more, their petition was written by attorneys representing the Center for Food Safety. The Center for Food Safety is a public-interest group that is “working to protect human health and the environment by curbing the use of harmful food production technologies and by promoting organic and other forms of sustainable agriculture” (Center for Food Safety, 2013).

Nutrition Facts			
Per 3/4 cup (175 g)			
Amount		% Daily Value	
Calories 160			
Fat 2.5 g		4 %	
Saturated 1.5 g		8 %	
+ Trans 0 g			
Cholesterol 10 mg			
Sodium 75 mg		3 %	
Carbohydrate 25 g		8 %	
Fibre 0 g		0 %	
Sugars 24 g			
Protein 8 g			
Vitamin A	2 %	Vitamin C	0 %
Calcium	20 %	Iron	0 %

Figure 1. Nutrition facts table (Health Canada, 2008).

Many groups are fighting to have GM foods labeled, but we have yet to see one fighting to label all cultivar-development methods, or—for example— water-usage rate per acre. If mandatory labeling will go beyond specific nutrient composition, there must be guidelines for what information beyond nutrient composition must be included, and they must be applied to all foods and at the same time. Figure 1 shows an example of the “Nutrition Facts” label required by Health Canada (2008) for all foods:

None of this information is of use to a consumer trying to make an informed, rational decision with regards to genetics, environment, or the economics of the production method. Other labeling options, which are fairly similar between the United States and Canada, include health claims that are convoluted for the average consumer. Also “Organic” or “Irradiated”—as words or symbols—may influence a consumer’s decision based on emotion rather than on rationality.

We propose a change to mandatory labeling of foods to include information on how the crop was produced and what, if any, modifications were made (Figure 2): It provides context to the consumer—in terms of cultivar-development technology, production method and environmental impact—enabling a wiser decision on whether to purchase. However, inconsistencies exist within this label. Whereas the “Irradiation” symbol is international, the “Organic” symbol is country-dependent, and there is no official international logo for GM or GE (genetically engineered), implying that common definitions of “organic”

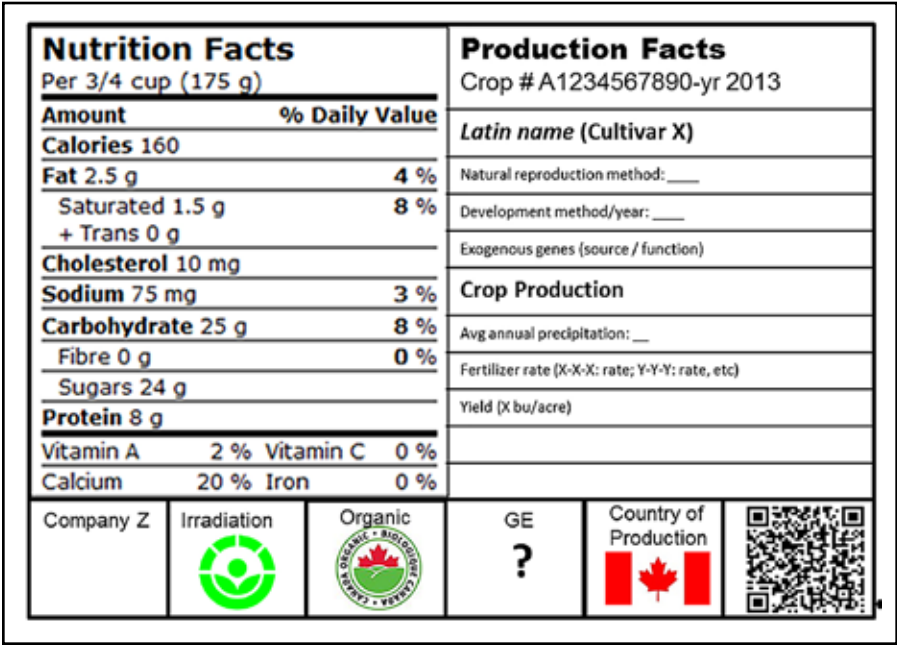


Figure 2: Nutrition Facts (Health Canada, 2008) with a proposed change to include crop-production data.



Figure 3: A QR code (Kaywa, 2013)

and “GMO” are yet to be reached. It seems imperative that international definitions and standards should be determined before discussions about labeling occur.

Another easy improvement to labeling would be quick-response (QR) two-dimensional bar-codes (Figure 3), which have been used for nearly twenty years in Japan. Extremely versatile, they can impart many types of data, including a website link to in-depth information. Although a specific application (“app”) is needed for downloading and a smartphone is required for scanning, the readers are available online free of charge (iTunes, 2013; Mobile-Barcodes.com, 2013;). Some 47% and 56% of Canadian and American adults now have smartphones (Ipsos, 2013; Pew Internet, 2013).

Once linked to a website, an abundance of information may be accessed. For example, the first link from the QR code may provide a simple sentence-long definition; at the end of that definition there may be an option to view an abstract about the same topic, and finally a third linked option may be available with an article or protocol about the technology. If the information is from an online unbiased database, such as PubMed², it would help build consumer trust.

²<http://www.ncbi.nlm.nih.gov/pubmed>.

Another opportunity for labeling change is serving size. If nutrition calculations were based on a consistent portion size, consumers could more readily compare products. This would be important in a situation where a GM crop undoubtedly demonstrates a nutritional advantage over a non-GM or organic competitor. As serving sizes exist now, consumers can easily be misled. Furthermore, certain websites could be more user-friendly. For example, the Health Canada website³ contains many fragmented, redundant labyrinths with a poor internal search engines; even the advanced search options often produce countless absurd results unrelated to the inserted keyword.

In mentioning these ideas during NABC 25, typical responses were “no,” and “labeling is already established.” This attitude perpetuates a stagnant mindset and accomplishes nothing. Obviously it will cost more initially, but there is so much potential to streamline the self-education system, that the cost should be examined from a long-term perspective. Ability to access information about all types of foods will empower consumers to have meaningful discussions with those in industry about legitimate concerns.

Many opponents of GMOs run stylish, yet simplified, advertising campaigns (Mercola, 2012). Of course, no credential pre-requisites are required to create an anti-GM website. Superficially, these sites may appear to be neutral, but within a few paragraphs of reading, the “anti” message becomes clear. Celebrity names may be mentioned (Afifi, 2012), current events in biology quoted (Latsch, 2007), and emotion used (Flores, 2013) to persuade the lay reader. It is necessary to investigate these sources to comprehend the scope of the challenge of properly educating the general public.

As food-label content and regulatory decisions with regards to food production are typically imposed by food manufacturers and/or the government, there is an urgent need to assemble a third-party arbitration group. Ideally, this group would include representatives of the government, industry, public-interest groups and lawyers. It could be responsible for final decisions on food labeling and on manufacturing and production standards. Primarily, it would assure the public of being minimally biased, reaching timely resolutions while maintaining the best interests of all stakeholders. Educational outreach programs could be facilitated by this group to foster a better-informed public. It would be best if such a group could be set up across national borders, as new ideas and perspectives are often gained in the absence of geographical constraints; otherwise, arbitration groups set up within each country should convene annually, at least, to discuss progress. The NABC-25 forum is a good example of how insight can be gained from this type of meeting.

To summarize, “genetic modification” and similar terms have negative connotations. A good example of what we can do to overcome this is the tactic being used by the creators of non-browning apples⁴ who are using a trademark to denote genetic modification (Arctic® apples; arcticapples.com, 2013). They are educating the public on how they made the apple, both on their website and in their talks to the public. This goes hand-in-hand with

³<http://www.hc-sc.gc.ca/index-eng.php>.

⁴Pages 87–94.

our proposal to make labels more educational. Voluntary labeling will bring goodwill and separation from the large biotech companies. We also need a unified voice to respond to spurious negative claims about the safety of GMOs and we need a social-media presence to combat adverse claims in real time. Opponents of GMOs, such as Greenpeace and Non-GMO, are pouring large amounts of money into fighting GMOs. We can combat this effectively only with calm, reasoned logic. Furthermore, it would not be appropriate for the voice of reason to be from industry; perhaps the NABC can be that voice.

Education

In the United States, there has been a decrease in science- and math-test scores over the last few years. This trend applies to students when tested from fourth to twelfth grades (National Center for Education Statistics, 2013). Furthermore, many students have little understanding of where food comes from or what it takes to grow crops and produce meat. This problem may be solved as follows:

- The first way is for scientific and mathematical organizations to come together and advocate to national, state/provincial, and local governments to stop decreasing spending on STEM⁵ education; potentially, this is a role that NABC can be a part of.
- The second way is for universities and scientific organizations to promote STEM and agricultural experiences for primary and secondary students, to educate on how food is grown and to show STEM in action. A good example of how this can be successfully accomplished is the outreach program administered by the Arkansas Center for Plant Powered Production (P3, 2013). One of the mission goals for P3 is to promote plant sciences in the state of Arkansas. P3 has developed plant-science kits, which science teachers can borrow, containing everything for a plant experiment, such as making biofuel. Additionally, P3 also recently sponsored a workshop for middle-school students in Jonesboro, AR, to come and transform a plant and extract DNA from strawberries. NABC-member institutions could promote similar programs in their respective areas and increase exposure of students to science.
- A third way that NABC could help to improve STEM education is to bring students to visit GMO trials so that they can see for themselves what these crops can do. By increasing the quality of STEM education and having an outreach to the public, we can begin to reverse the negative public perception of GMOs.

Funding

The state of STEM funding in North America is discouraging. Due to budget cuts, funding for research has been drastically decreased in the United States. For example, the NIH budget for 2013 was reduced significantly and is lower than for FY 2003 by 22%, or about \$4.7 billion (aaas.org, 2013). Most other agencies have had minor cuts or stayed about the same. Details for FY 2014 have not been finalized yet, but more cuts are

⁵Science, technology, engineering and mathematics.

⁶\$5.7 billion with adjustment for inflation.

expected based on the US House of Representatives budget (faseb.org, 2013). If the NIH budgetary trend is an indication, then funding opportunities will be greatly reduced and the number of new projects funded severely cut. As emerging scientists, we feel that this trend will negatively impact both innovation and advancement. If the US government had not funded the \$3.6 billion⁶ Human Genome Project in 1988, we would not be seeing the renaissance of genetics and the related “-omic” branches that have led to \$1 trillion worth of biotechnology companies. Given that there is a high return on research-funding investment (at least a 30% return and up to 100%), we are not only short-changing ourselves but also future generations (Center for American Progress, 2012). The NABC must stand with other scientific organizations, and concerned citizens, to stop the slashing of research funding currently occurring in Washington.

CONCLUSIONS

NABC is composed mainly of universities and does not have the “baggage” in promoting GMOs so commonly observed in industry. NABC is uniquely positioned to be a voice of reason in promoting the benefits of GMOs:

- Increase interdisciplinary and international communication
- Take advantage of media outlets available for either educating or advertising, at least to counter the anti-GMO movement that utilizes these tools already
- Find a pro-GMO celebrity with a large following to promote GMO techniques, or at least for proper education about GMOs
- Revamp food labeling to present official information about all foods in a comparable manner
- Establish a third-party arbitration group responsible for labeling, educating, and dispute resolution
- Get more involved in early education to increase the number of students that are interested in STEM
- Advocate for increased funding for STEM research or at the very least no further reductions in research funding

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Responses of Selected Garden Roses to Cyclic Drought Stress and Four Different Soil Moisture Contents

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Greenhouse studies were conducted to evaluate the response of four garden roses (*Rosa* × *hybrid* L.), ‘RADrazz’, ‘Belinda’s Dream’, ‘Old Blush’, and ‘Maria Pavie’, to cyclic drought stress (Experiment I) and two garden roses, ‘RADrazz’ and ‘Belinda’s Dream’, to four constant soil moisture contents (SMC) (Experiment II). In Experiment I, plants grown in containers with a peat-based substrate were subjected to two watering treatments, well watered (30–40% SMC) and cyclic drought stress. The cyclic drought stress was induced by watering the plants to container capacity (around 40% SMC) and then withholding irrigation until container weight reached a predetermined value and plants exhibited incipient wilting (around 10% SMC). In Experiment II, an automatic irrigation system was set up to maintain four constant SMC levels, *i.e.* 10, 20, 30, and 40%. Two cultivars were grown in containers with a peat moss-pine bark based substrate. In Experiment I, shoot growth and flower number were reduced in the drought treatment compared to the well-watered control in four cultivars. Net photosynthetic rate (P_n), stomatal conductance (g_s), transpiration rate (E), and mid-day water potential of four cultivars decreased as substrate moisture content decreased. In Experiment II, there was a 90% reduction in water application at 10% SMC compared to 40% SMC during the two-month treatment period. In both cultivars, there were no significant differences in growth and physiological responses between 30% and 40% SMC. Photosynthesis was highest at 30 and 40% SMC and lowest at 10% SMC in both cultivars. In ‘RADrazz’, shoot DW was reduced by 20.7% and 87.3%, root DW was reduced by 34.1% and 82.1%, while flower number was reduced by 27.5% and 87.8% at 20 and 10% SMC,

respectively, compared to 30% and 40% SMC. In 'Belinda's Dream,' shoot DW was reduced by 30.7% and 87.6%, root DW was reduced by 46.8% and 83.5%, while flower number was reduced by 41.9% and 77.1% at 20 and 10% SMC, respectively, compared to 30% and 40% SMC. In summary, 'RADrazz' was considered to be more tolerant to drought compared to the other three cultivars with its least reduction in shoot and root growth, flower number, and gas exchange under drought stress. Plants at 30 and 40% SMC maintained the highest shoot and root DW, flower number, midday leaf water potential, and photosynthesis. Water applied at 30% and 20% SMC was reduced by 31% and 70%, compared to 40% SMC, with excellent performance at 30% SMC and acceptable growth and quality at 20% SMC. The 10% SMC led to significant growth reduction, poor quality, and 25% mortality.

Characterization of Rosa spp. Breeding Populations to Black Spot for QTL Identification

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Black spot disease, caused by the fungus *Diplocarpon rosae* Wolf, is the most serious disease of landscape roses (*Rosa hybrid* L.) worldwide. Dominant genes for complete resistance to specific races of the pathogen were identified in roses as *Rdrs*. From a breeding perspective, a rapid screening of potential hybrid materials by molecular markers is beneficial for identifying the resistant germplasm efficiently. Although partial resistance has also been documented, the responsible QTLs remain unidentified. In this project, responses to *D. rosae* of 16 genotypes of roses that were used as parents in hybrids were characterized with two inoculation methods: the detached leaf assay (DLA) and the whole-plant-inoculation (WPI) method. The correlation between the relative resistances among genotypes as determined by each method was analyzed. Although DLA is more sensitive than WPI in measuring relative resistance, the correlation among the two methods is high ($r^2 > 0.8$), which indicates that either can be utilized to characterize *D. rosae*. Six diploid hybrid populations which are segregating for strong partial resistance derived from *Rosa wichurana* have been planted in the field for black-spot evaluations. These plants were also measured by DLA for resistance to race 8. The phenotypic data will be combined with the genotyping data for the populations to identify QTLs for partial resistance to black spot.

Index words: *Rosa*, Black spot, Disease resistance, *Diplocarpon rosae*, QTL, host-plant resistance

Understanding Plant Responses to Water Deficit Conditions: A Systems Biology Approach

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The staggering growth in population, with no expansion for arable land, provides enormous pressure to increase food production. However, food production is seriously hampered by abiotic stresses such as drought. To address this issue, crop tolerance to drought must be improved. In order to develop strategies to improve plant responses to water stress, one must understand the regulatory pathways involved in plant responses to water stress. Using tobacco as our model, we analyzed the spatial and temporal transcriptome and metabolome profiles of plants subjected to water stress at different time points (20, 40, 60, 120 and 240 min). The transcriptome profile showed major transcription factor families such as ERF, WRKY, NAC, bHLH and MYB to be highly induced by water stress in both roots and leaves. Downstream genes such as late embryogenesis abundant proteins (LEA), dehydrins, aquaporins, raffinose synthase and galactinol synthase were also highly induced. The gene-expression profile showed that the gene products from the stress-inducible genes can be grouped as regulatory proteins and proteins involved in direct protection of the cell from stress.

Metabolome profile showed accumulation of proteinogenic amino acids as well as compatible solutes such as proline, trehalose and raffinose. The expression profile of our target genes concurred with our metabolome profile.

The Effect of “Microbial Fermented High Protein Soybean Meal” (FSBM), as a Fishmeal Replacer, on Functional Properties of Twin-Screw Extruded Aquadiet

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Fast-paced growth in global aquaculture has elevated concerns about the high costs of aquafarm production and potential water pollution. Thus, finding eco-friendly and more sustainable alternative protein sources for fish diets is of vital importance to the industry. A twin-screw extrusion processing study was performed using three ingredient blends formulated with graded levels of FSBM (0, 80% and 100% db) as the fishmeal replacer, in combination with appropriate amounts of other required ingredients for rainbow trout diets. To obtain cohesive extrudates, extrusion processing conditions (conditioner steam, extruder water, and screw speed) were varied. The effect of FSBM inclusion on functional properties of the extruded diets [moisture content (MC), water activity (aw), thermal properties, expansion ratio (ER), unit density (UD), bulk density (BD), water absorption (WAI), solubility (WSI), durability (PDI) indices, and color] were extensively evaluated. Increasing the FSBM content from 0% to 100% resulted in a substantial increase in brightness, greenness, and yellowness, and a decrease in BD, WAI, and UD values of the extrudates by 12.5%, 73%, 30%, 7.3%, 27.5%, and 10%, respectively. Compared to the control diet (100% fishmeal-based), extrudate moisture contents increased by 15.2% and 22% for the diets containing 80 and 100% FSBM, respectively, although no change was observed by increasing FSBM from 80 to 100%. The highest WSI was obtained for 80% FSBM inclusion; however, further increasing FSBM did not influence the WSI significantly. All extrudates represented a low risk of microbial contamination, and high mechanical strength due to low aw and high PDI values (<0.5% and >99.5%, respectively). The most buoyant extrudates were obtained using total FSBM inclusion, with UD and ER values of nearly 660 kg/m³ and 1.3, respectively. Overall, the results indicated that FSBM can be a promising protein alternative in rainbow-trout feed production.

Keywords Aquaculture, Extrusion, Microbial fermented soybean meal, Rainbow trout, Twin-screw Extruder

Effect of Glutamine Synthetase Overexpression on the Growth and Biomass Production in Sorghum Growing Under Different Nitrogen Conditions

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Nitrogen is a primary macronutrient for plants and plays a critical role in plant growth and crop productivity. However, it is estimated that only between 30% to 50% of applied nitrogen is taken up by plants, with the remainder contaminating soil, water and air. Therefore, from both economic and environmental standpoints, there is considerable interest in developing plants that take-up and use nitrogen in a more efficient manner. In this study, we investigated the effects of glutamine synthetase (GS) overexpression on the growth and biomass-production in sorghum (*Sorghum bicolor* L.) under low and optimal nitrogen availability. GS is an enzyme involved in nitrogen metabolism and catalyzes the ATP-dependent reaction between ammonia and glutamate to produce glutamine. The 1,071 bp long coding sequence of a sorghum cytosolic glutamine synthetase gene (*gln1*) was ligated at the 3'-end of the maize ubiquitin promoter, and this construct was introduced into sorghum by *Agrobacterium*-mediated transformation of immature embryos. T2 generation transgenic plants growing under optimal nitrogen conditions showed a reduction in the number of seeds present in the primary tiller, but exhibited a significant increase in the shoot vegetative biomass due to an accelerated formation of the secondary tillers compared to the wild-type counterparts. The number of seeds in these secondary tillers was higher than that in the primary tillers of the transformants. Thus, at the termination of the experiment (35 days post anthesis in primary tiller), significantly higher number of seeds was produced by the transformants. In contrast, no differences in growth or developmental parameters were observed between the transformants and wild-type grown under low nitrogen conditions. Our findings suggest that overexpression of *gln1* in sorghum affects the physiological response of the plant to nitrogen availability, leading to enhanced grain yield and biomass accumulation under optimal nitrogen levels.

Microarray Analysis of Soybean Cultivars Under Salt Stress to Identify Differentially Expressed Genes

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With a worldwide increase in irrigation and agricultural expansion into marginal lands, saline soils are increasingly problematic for farmers. Soybean, *Glycine max* (L.) Merr., cultivars can react differently to salt stress; soybean lines that accumulate chloride in the leaves are typically salt sensitive and those that exclude chloride from the leaves are generally more salt tolerant. Current efforts in developing salt tolerance focuses on breeding and screening for chloride sensitivity. A cisgenic approach would be much faster without the yield drag that can accompany conventional breeding. However, the genetic basis and the exact mechanism for salt tolerance are currently unknown. The first step in developing a salt-tolerant cisgenic soybean is to identify the genes involved in salt tolerance. To identify genes differentially expressed in response to salt stress, the chloride-sensitive cultivar Clark, and the chloride-tolerant cultivar Manokin were compared in whole transcriptome studies. Plants were flooded daily with 100 mM NaCl or H₂O for six days. On the sixth day, leaf tissue was collected, total RNA was extracted and subjected to transcriptome analysis on a whole soybean transcriptome Affymetrix GeneChip®. The resulting data were analyzed in a Multiple Experiment Viewer and JMP®. In total, 119 genes in Clark and 54 genes in Manokin were differentially expressed in response to salt stress. A two-way ANOVA identified 387 genes that were differentially regulated between Clark and Manokin either treated with H₂O or NaCl. Select genes that were differentially regulated in response to salt stress in Clark and Manokin were verified with reverse transcription (RT)-PCR and RT-qPCR. Identification of the genes involved in salt tolerance in soybean excluders is the first step in generating a stable, salt-tolerant cisgenic soybean. Candidate genes were identified and future work will focus on their roles in soybean salt tolerance.

Molecular Analysis and Characterization of the Gene(s) Involved in the Biosynthesis of 15-OH 18:2-9,12 Hydroxy Fatty Acid in Avena (Oat)

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Oat is the only known source of 15(R)-hydroxy-(9Z),(12Z)-octadecadienoic acid (15-OH 18:2-9,12) which is believed to be enzymatically derived from linoleic acid (LA) in developing seed tissue. The properties of a hydroxy fatty acid (HFA) have negative gastrointestinal effects once consumed, and thus minimal HFA levels are desirable. For non-food purposes, HFAs have properties ideal for replacing petroleum-based products, so high levels are ideal. The ability to increase the levels of HFAs to economically significant amounts, or to eliminate them for food purposes, may require the genetic optimization of crops. Determining the genetic sequence of the gene(s) involved in producing the Δ 15-linoleate hydroxylase (FAH15) that results in this unusual fatty acid (UFA) may lead to a new crop with the capacity for a customized fatty acid (FA) profile at industrial-scale production levels and making economic sense. Novel genetic information will also enhance marker-assisted breeding.

The putative FA hydroxylase is believed to share high similarity to a fatty acid desaturase (FAD) that acts upon the same position of the LA substrate as that of the putative FAH. Using bioinformatic software, previously-characterized FAD3 sequences from other species were queried against oat developing seed expressed sequence tags (ESTs), to determine putative oat *fah* contigs on which to base the subsequent experiments.

After synthesizing mRNA-derived cDNA, the gene was amplified with PCR and selected for after transforming *Escherichia coli* (*E. coli*) with a recombinant intermediate vector and gene of interest; this was followed by ligation into a eukaryotic expression vector. Currently, expression in *Saccharomyces cerevisiae* is being performed to observe hydroxylase functionality. Expression will be confirmed via presence of the gene's product, 15-OH 18:2-9,12, using gas chromatography/mass spectrometry (GC/MS) analysis.

*Early Breeding and Genetic Work for Developing *Vigna unguiculata* (L.) Walp. (Cowpea) Lines Tolerant of the Phosphorus-Poor Soils of Sub-Saharan West Africa*

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In the United States, two types of *Vigna unguiculata* (L.) Walp. (cowpea) are consumed as seed: black-eyed peas and purple hull peas. In Sub-Saharan Africa, cowpea is a widespread staple crop consumed for all components—leaves, pods, and seed—both by people and by livestock. However, soils of West Africa are poor in phosphorus (P), a soil macronutrient all crops need for growth. The cost of using P reserves to produce fertilizer with P is too high for developing countries in Africa, and thus fertilizer with P is not readily available. The purpose of this research is to start breeding and genetic work for the development of cowpea lines that grow well in low-P soils. At least three cowpea varieties have been successfully identified with measurable tolerance as estimated by shoot biomass in a hydroponic screening method. Both tolerant and susceptible varieties have been further analyzed for seed P, root biomass, internal shoot-P content, and internal root-P content to gain basic physiological insight into cowpea varieties' tolerance of P deficiency. This research lays the foundation for determining genes or quantitative trait loci (QTL) responsible for cowpea's tolerance of low-P soils. F_2 , BC_1 and recombinant inbred line (RIL) populations have been developed from 'high \times low' crosses of lines for their tolerance of low-P soils. F_2 s and BC_1 s have been screened for tolerance to understand the genetic control of the trait. The RILs will be used to begin QTL mapping using simple sequence repeat (SSR) and single nucleotide polymorphism (SNP) markers. QTL mapping will give a potential foundation for future marker-assisted selection (MAS) of the low-P-tolerance trait in cowpea and other crops.

Graphic Mapping of Molecular Markers Related to Fiber Production in Sugarcane

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Sugarcane is a complex polyploid and aneuploid species, which makes genomic studies a huge challenge. This crop is economically important because it is the main source of both sugar and ethanol production. In sugarcane-breeding programs, functional markers can be used to accelerate the process and select important agronomic traits. Besides this practical application, molecular markers are also suitable to study the genetic architecture of complex agronomic traits (quantitative traits) that can be resolved into single Mendelian components. The advent of next-generation DNA-sequencing (NGS) technologies has led to the development of rapid genome-wide single nucleotide polymorphism (SNP) detection, which can be applied to mapping and characterization of traits of interest in larger populations. Such an approach, where sequences are used simultaneously to detect and score SNPs, is known as genotyping-by-sequencing (GBS). One of its main advantages is the ability to use the genetic maps generated using GBS-based sequencing information subsequently for identifying loci of interest from different sets of individuals, including segregating populations or mutant pools.

The aim of this work is to identify microsatellite markers and SNPs associated with lignin and cellulose in sugarcane. The mapping population is composed of 250 individuals derived from a bi-parental cross between two elite clones from CTC's (Center of Sugarcane Technology) breeding program in Brazil. We already tested 18 microsatellites developed from a Sugarcane EST database (SUCEST), which generated 24 potential markers to be mapped. The results that will be generated in this study will increase the probability of development of functional SNPs and microsatellites associated with important agronomic traits for sugarcane-breeding programs.

*The Influence of Leaf Epicuticular Wax on Stomatal Conductance, Light Reflectance, Canopy Temperature, and Chlorophyll Content in Long-Term High-Temperature-Stressed Spring Wheat (*Triticum aestivum*)*

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Leaf epicuticular wax (EW) acts as a barrier between leaf tissue and the surrounding environment. EW protects the leaf from fungal attack, moisture loss from stomates, as well as excess heat, and radiation. Preliminary tests have identified the influence of EW in decreasing the heat-susceptible index (HSI), leaf-canopy temperature (CT), and improving total yields of wheat (*Triticum aestivum*). Most cultivars show the presence of leaf EW, but its role in improving high-temperature-stress tolerance during reproductive stages has yet to be defined. This study seeks to provide insight to the behavior of flag-leaf EW during different reproductive stages of wheat cultivars. Different glaucous wheat cultivars were studied in the greenhouse, exposed to a high-temperature treatment (21°C-night and 38°C-day) during 2013. Leaf EW discs and physiological data (transpiration, chlorophyll fluorescence (CF), reflectance, leaf CT) were collected every 3rd day after head initiation to the 15th day after pollination (DAP). The marked results were a significant increase in EW load on the flag leaf from head initiation to 15 DAP. CF remained constant from 10 DAP to 15 DAP, conferring chlorophyll content was not much significantly decreased. Transpiration was significantly lower at 10 DAP compared to 3 DAFE (days after head emergence) and 15 DAP. Presence of EW statistically influences percent reflectance between 700 nm to 1120 nm wavelength. The cultivars 'Seri M82' 'Len' and 'Halberd' exhibited high levels of leaf EW and low adaxial transpiration under high temperature. Leaf adaxial surface had significantly higher transpiration compared to abaxial surface. Leaf epicuticular wax of 'Seri M82' showed a strong correlation with CT, leaf temperature depression, abaxial transpiration, and CF.

Abscisic Acid: A New Management Tool for Vegetable Transplants

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Abscisic acid (ABA) is a plant hormone that triggers adaptive responses to water stress, including stomatal closure, inhibition of leaf expansion, and promotion of primary-root elongation. Using these growth modulations, our goal is to produce high-quality, more-stress-tolerant vegetable transplants. First, we examined the stress control effect of ABA. In muskmelon (*Cucumis melo* L.) seedlings subjected to water withholding, pre-stress treatment of ABA (0.2 to 7.6 mM) improved the maintenance of leaf relative water content by limiting transpirational water loss. Upon rewatering, the ABA-treated seedlings showed faster photosynthetic recovery and greater dry-matter accumulation than the control. Second, we examined ABA as a growth-holding agent to extend the marketable period of transplants. When jalapeno (*Capsicum annuum* L.) seedlings were treated with ABA (3.8 mM) at marketable size and extendedly grown in a greenhouse, excess stem elongation and leaf expansion were reduced by up to 17 and 3 days, respectively. The relatively rapid recovery of leaf area is important to avoid long-term growth inhibition, and thus its cellular basis was studied in arabidopsis (*Arabidopsis thaliana*). Whereas ABA (1 mM) inhibited leaf expansion of young developing leaves, it had no effect on epidermal cell division, suggesting that ABA inhibits leaf expansion solely by limiting cell expansion. More importantly, the maintenance of cell division may enable transient leaf-area adjustment without limiting plant-growth capacity. Finally, we examined the role of ABA in root growth using ABA-deficient mutants (*aba2-1* and *nced3-2*) of arabidopsis. Although ABA (1 μ M) promoted primary root elongation both of the wild type and mutants, its effect was more pronounced in *nced3-2* than in the wild type under moderate water stress (–1 MPa). These results suggest that ABA can be used as a new growth regulator for improved stress control and extended marketability in vegetable transplants.

Does Ethylene Alter the Regulation of Health-Promoting Compounds in Grapefruit?

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Grapefruit (*Citrus paradisi* Macf.) is a rich source of bioactive compounds including flavonoids and furocoumarins that have demonstrated various health-promoting properties such as anti-inflammatory, anti-proliferative, and anti-carcinogenic as well as affecting absorption of certain medications. These bioactive compounds are influenced by various pre-harvest and post-harvest treatments. Early-season grapefruits are degreened using ethylene to promote peel color change from green to reddish orange. It is critical to study the effect of ethylene on biosynthesis of flavonoids and furocoumarins. In our preliminary study, ethylene treatment appeared to change the levels of flavonoids and furocoumarins in the Rio Red grapefruit pulp. Flavonoids namely narirutin, naringin, neohesperidin, didymin and poncirin significantly increased ($P < 0.05$) in degreened fruits at 7 days of storage. Non-degreened (control) fruits had significantly higher content of furocoumarins including 6',7'-dihydroxybergamottin (DHB) and bergamottin at 7 days; however, at 14 and 21 days, furocoumarins were significantly higher in degreened fruits. To further understand how ethylene affects the regulation of flavonoid and furocoumarin biosynthesis, three major genes namely phenylalanine ammonia lyase (PAL), chalcone synthase (CHS) and S-adenosyl-L-methionine:bergaptol *O*-methyltransferase (SAM-BMT) were selected. Using a rapid amplification of cDNA ends approach, the full-length cDNAs of PAL and CHS were isolated and cloned from Rio Red grapefruit, and the SAM-BMT gene will be cloned. The alignment of amino acid sequence of grapefruit CHS showed 99.2% similarity with CHS1 and 98.2% with CHS3 of *Citrus sinensis*. The transcriptional activities of these genes after ethylene treatment will be investigated using quantitative real-time PCR. This project is based upon work supported by the USDA-NIFA # 2010-34402-20875 "Designing Foods for Health" through the Vegetable and Fruit Improvement Center.

Impact of Undergraduate Students on Biotechnology Research at the Vegetable and Fruit Improvement Center, Texas A&M AgriLife Research: Gene Discovery, Molecular Marker Development and Genetic Transformation Associated with Bioactive Compounds

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Melons rank among the top five most frequently purchased fruits in the United States. Because of consumers' increased interest in enhanced nutrition and chemopreventive properties, breeders have focused on developing fruit and vegetable cultivars with enhanced health-promoting compounds. The research at the Vegetable and Fruit Improvement Center-Plant Biotechnology Core Unit mainly focuses on gene discovery, molecular-marker development and genetic transformation, in order to help breeders rapidly and effectively introduce key traits into elite varieties. The objectives are to identify candidate genes and develop molecular markers associated with bioactive compounds. This study examined the mechanisms of carotenoid regulation and found that lycopene beta-cyclase (*LCYB*) may be crucial for conditioning flesh color differences between red and canary-yellow watermelons. Polymorphic sequences were identified in the promoters and developed into a PCR-based marker for selection of *LCYB* alleles. In addition, a single nucleotide polymorphism (SNP) was identified in the coding region of carotenoid isomerase (*CRT*) of red and salmon-yellow watermelon; this SNP results in substitution of a conserved leucine to proline. The *CRT* SNP co-segregated with salmon-yellow flesh color, suggesting that *CRT* may be essential for lycopene accumulation in watermelon.

In addition, watermelon phytoene synthase C was introduced into an elite honeydew to elevate beta-carotene. Altered phenotypes were observed in rinds of transgenic lines, and biochemical assays showed that beta-carotene and phytoene were elevated. Elucidating carotenoid regulation mechanism and developing molecular markers will provide useful tools to enable rapid breeding of novel watermelon varieties with enhanced profiles of health-promoting bioactive compounds. Importantly, undergraduate students participated fully in all aspects of this research, gaining research experience and hands-on training in molecular techniques, biochemical analyses, and genetic transformation. The present report is based on work supported by “Designing Foods for Health,” USDA CSREES Grant # 2010-34402-20875.

Bitter Melon (Momoridica charantia): A Potential New Vegetable in Texas and its Antidiabetic Properties

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Several studies have reported bitter melon to possess various health-promoting properties such as anti-oxidant, anti-bacterial, anti-cancer and anti-diabetic activities. Relatively few studies have attempted to evaluate the positive health effects of individual purified compounds isolated from bitter melon. The goal of this multi-faceted study is to identify the phytochemical constituents of bitter melon fruit and seeds responsible for anti-diabetic and anticancer properties. Data presented here illustrate the ability of bitter melon methanolic extract to inhibit α -amylase (82–99% inhibition), an enzyme present in the intestine responsible for breaking down polysaccharides into absorbable glucose units. The amount of inhibition was comparable to the current type-2 diabetes-management synthetic drug, acarbose. Furthermore, higher total phenolics were found in bitter melon fruit that was dried under refrigerated conditions versus higher temperature-drying techniques. Currently, two compounds have been isolated from bitter melon fruits by flash chromatography. The future directions of this study involve the quantification of these health-promoting compounds in several varieties, the fluctuation of these compounds due to various pre- and post-harvest treatments, vegetative propagation strategy for the production of phytochemical-dense plants and optimal growing strategies for Texas. Lastly, gene expression will be explored for the possibility of production of anti-diabetic triterpenoids in tissue culture. This project is based upon work supported by the USDA-NIFA # 2010-34402-20875 “Designing Foods for Health” through the Vegetable and Fruit Improvement Center.

Microplate Reader: A Rapid Tool in an Onion-Breeding Program to Determine Quality

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Onions are the second highest-valued horticultural crop produced in the United States. They are valued for their distinctive flavor and recognized for their potential health benefits. Pungency of onions is a major criterion for economic remuneration and it can be quantified by measuring enzymatically produced pyruvic acid. Conventional methods of pyruvate measurement have certain limitations in terms of stability of the colorimetric reaction leading to inaccurate quantification. The pyruvic acid content is significantly influenced by variety, location, and interaction with the environment. Approximately 80% of the total variation is genetic, which is a major problem to the producers in maintaining uniform quality in mild onions. Therefore, accurate measurement of pyruvic acid is critical. In the present study, a rapid colorimetric method was developed to determine pyruvic acid in onions by reacting the onion sample with 2, 4-dinitrophenylhydrazine (DNPH). The absorbance of the colored complex was measured at $\lambda 485$ nm using a microplate reader. The developed method was used to determine the levels of pyruvic acid in different onion cultivars. The observed pungency for red onion is 11.20 ± 1.89 mM, yellow onions being less pungent with 10.34 ± 0.93 mM, white onions having lesser pungency with $6.05 \text{ mM} \pm 1.53$ and honey sweet onions with the least pungency of 4.37 ± 1.22 mM. The use of a strong base enhanced the stability of the colored complex for up to two hours. The developed method is simple, robust, economical and reproducible for analysis of pungency in onion breeding programs within a short duration of time. This project is based upon work supported by the USDA-NIFA # 2010-34402-20875 "Designing Foods for Health" through the Vegetable and Fruit Improvement Center.

Flash Chromatographic Separation of Limonoids from Dancy Tangerine

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Dancy tangerine (*Citrus tangerina*) is a popular citrus variety that produces a bright-orange, easy-to-peel fruit. In recent years, due to their taste and quality characteristics, a rapidly increasing trend in their production is noticed. Apart from their sensory attributes, they also contain a wide array of biologically beneficial health-promoting compounds such as limonoids, flavonoids, amines, carotenoids, and organic acids. Specifically, limonoids have been further investigated for their health benefits and pharmacological uses such as: antibacterial, antifungal, antiviral, and anticarcinogenic activities. In order to provide proof-of-concept, limonoids need to be tested in animal- and human-intervention trials, which require an isolation and purification method that is cost-effective, rapid, and repeatable. The seeds and carpel membranes—waste byproducts of the citrus juice industry—are among several sources commonly used to isolate and characterize bioactive compounds. Utilizing these byproducts provides an economical resource for purification of health-promoting compounds. Furthermore, flash chromatography can be used to isolate compounds of high purity in a short time in comparison to the traditional method of open column chromatography. Limonoids were extracted from Dancy tangerine seeds using ethyl acetate resulting in a condensed, crude product. Silica gel was used to impregnate the samples which were then subjected to flash separation. Fractions were pooled based on retention times from individual fractions of high-pressure liquid chromatography (HPLC) analysis which led to three compounds: obacunone, limonin, and deacetyl nomilin. To the best of our knowledge, this is the first study on flash chromatography separation of limonoids from Dancy tangerines in multi-gram quantities.

High Tunnel for a Specialty Crop: Strawberry Production in Texas

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Six commercial cultivars of strawberry (Albion, Chandler, Festival, Radiance, San Andrea's, Seascape) were grown in high tunnels and in the open field at Lubbock, TX. At maturity, fruits with similar size and shape were harvested and analyzed for quality (sugars and titratable acidity), total phenolic content (Folin Ciocalteu assay) and radical scavenging activity (DPPH assay). Strawberries grown in high tunnels showed higher levels of sucrose and fructose. No major effect of the production system was noticed on the level of glucose or titratable acidity. Chandler, Festival and San Andreas varieties had significantly higher levels of total phenolic in comparison to other varieties. Chandler, Festival, San Andreas and Seascape had significantly higher levels of radical-scavenging activity as compared to Albion and Radiance varieties. However, no clear trend on the effect of high-tunnel cultivation as compared to field cultivation was noticed in the total phenolic content or radical-scavenging activity. These results suggest that high-tunnel cultivation could be an effective strategy for cultivating specialty strawberry with better quality and maintenance of phenolic content and radical-scavenging activity.

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NORTH AMERICAN AGRICULTURAL BIOTECHNOLOGY COUNCIL REPORT



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Providing an open forum for exploring issues in agricultural biotechnology

NABC REPORT 25

Biotechnology and North American Specialty Crops: Linking Research, Regulation, and Stakeholders

Proceedings of the twenty-fifth annual conference
of the North American Agricultural Biotechnology
Council, hosted by Texas A&M University,
June 4–6, 2013

Edited by
Allan Eaglesham and Ralph W.F. Hardy

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NABC Report 25

Biotechnology and North American Specialty Crops: Linking Research, Regulation, and Stakeholders

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Providing an open forum for exploring issues in agricultural biotechnology

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Thanks are due to the planning committee¹ (Rusty Carter, Heather Hirsch, Brenda Stone, Misty Vidrine, Carl Muntean, John Chivvis, Valerie Weber, Bill McCutchen, Bob Avant and Jackie Slovacek), to student workers (Maddie Kostroun, Cheyne Grey and Gus Sanchez) and to ANRP² student interns (Monica Hoz De Vila, Andrea Fonseca, Morgan Head, Dillon Garr, Shiloh Perry and Arlene Kent).

Smooth operation of the conference resulted from the contributions of the following:

Session Moderators: Dan Wineberger, David Baltensperger, Daniel Leskovar and Steve Pueppke.

Workshop Facilitators and Recorders: Peter Schuerman, Dan Lineberger, Daniel Leskovar, Frank Dainello, Bob Avant, Adam Helms and Andrea Kuban.

Student Voice Program Administrator: Susanne Lipari.

Student Voice Reporters: Matthew Bernard and Alma Laney.

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* * *

On behalf of NABC, we thank Graham Scoles (University of Saskatchewan) for first-rate leadership as NABC's chair, 2011–2013.

Ralph W.F. Hardy
President
NABC

Allan Eaglesham
Executive Director
NABC

December 2013

¹RWFH and AE also served on the planning committee.

²Agricultural and Natural Resources Policy Internship Program.

PREFACE

Taxpayers in the United States have invested heavily in public-sector research in agricultural biotechnology to provide more-sustainable and productive crops and safe and nutritious foods. Since the mid-1980s, scientists at the USDA and in university and small private laboratories have developed a broad range of genetically engineered (GE) varieties of specialty crops with useful traits including enhanced tolerances of biotic and abiotic stresses and improved nutrition¹. Almost a thousand different GE lines of small-market and specialty crops¹ were among the almost 17,000 regulated field trials approved by USDA since 1987².

In spite of this large public investment—as well as early technical successes and promising results in field trials—only a few GE specialty crops developed in public institutions have been released to date:

- Virus-resistant papaya
- A now defunct flax intended to be used for bioremediation
- Virus-resistant plum

These are very sparse returns considering substantial public investment over a quarter century. In fact, the majority of scientists at public institutions do not even consider further development of GE crops for commercial utility, even for traits that could advance agricultural systems, improve human health and help feed the increasing global population. On the other hand, there are signs that this trend is changing. Several transgenic events in specialty crops, are now moving towards commercialization as a result of collaborative efforts involving universities, industry, and regulatory agencies.

Furthermore, the Farm Bill—passed in February 2014—has restored the Specialty Crop Research Initiative funding, to about \$80 million per year³. We are pleased with this reemphasis of the fundamental importance of research in specialty crops, consistent with the focus of NABC's twenty-fifth annual conference.

NABC 25—held at Texas A&M University, College Station, June 4–6, 2013—brought together academic researchers, industry leaders, and government officials to discuss the roles of genomic sciences, regulatory policy and related topics in an attempt to catalyze increased agricultural progress, especially as it relates to specialty crops.

¹Miller J Bradford K (2010) The regulatory bottleneck for biotech specialty crops. *Nature Biotechnology* 28(10) 1012–1014.

²Anonymous (2014) Information Systems for Biotechnology: A National Resource in Agbiotech Information—USDA Field Tests of GM Crops. <http://gophisb.biochem.vt.edu/search-release-data.aspx>

³<http://www.thepacker.com/fruit-vegetable-news/Senate-passes-farm-bill-243553121.html#sthash.19Xbcib1.dpuf>.

To foster discussion, NABC 25 was organized under five topics:

- Opportunities and Challenges for Specialty Crops
- Genetic Engineering and Specialty-Crop Improvement
- Case Studies
- The Regulatory Process and Technology Access
- Perspectives from Relevant Groups

The final session on the morning of the third day focused on “Next Steps.” Speakers Tony Shelton (Cornell), Thomas Redick (Global Environmental Ethics Counsel) and Neal Carter (Okanagan Specialty Fruits) formed a panel along with conference host Bill McCutchen (Texas A&M). The discussion, which involved audience contributions, was moderated by Steve Pueppke (Michigan State). Salient points emerging from the “Next Steps” exchanges are included in a “conference overview” chapter.

A poster session was held on the evening of the first day. Prizes totaling \$5,000 were awarded to the five best poster presentations (\$1,500–\$500).

Participants in the *Student Voice at NABC* program⁴ attended the keynote and plenary sessions and met as a group on the second evening to discuss issues that emerged from the conference subject matter.

This volume contains the conference overview, manuscripts generated from transcripts of the verbal presentations by the speakers (see Contents on pages ix–x for the full speaker list), transcripts of Q&A sessions, which included audience participation, the *Student Voice* report, and abstracts from the posters.

NABC’s twenty-sixth conference—*New DNA-Editing Approaches: Methods, Applications and Policy for Agriculture*—will be held October 8–9, 2014, in Ithaca, NY, hosted by Cornell University and the Boyce Thompson Institute.

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Figures are printed in grayscale, hence information may have been lost from graphics lifted from colored PowerPoint slides. Color versions of the figures are available at http://nabc.cals.cornell.edu/Publications/Reports/pubs_reports_25.htm.

⁴The *Student Voice at NABC* program provides grants of up to \$750 to graduate students at NABC-member institutions (one student per institution) to offset travel and lodging expenses. Also, registration fees are waived for grant winners. Information on the *Student Voice at NABC 26* will be available at <http://nabc.cals.cornell.edu/StudentVoice.htm>.

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